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# Bimetallic oxidation catalysts

Gelling, Onko Jan

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RIJKSUNIVERSITEIT GRONINGEN

# BIMETALLIC OXIDATION CATALYSTS

**PROEFSCHRIFT**

ter verkrijging van het doctoraat in de Wiskunde en Natuurwetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de Rector Magnificus Dr. L.J. Engels
in het openbaar te verdedigen op vrijdag 14 september 1990
des namiddags te 4.00 uur
door

**ONKO JAN GELLING**

geboren op 11 juni 1964 te Lemmer

PROMOTORES : PROF. DR. B.L. FERINGA
PROF. DR. H. WIJNBERG

## Voorwoord

Met het tot stand komen van dit proefschrift beëindig ik een periode waarop ik met zeer veel genoegen terugkijk. Niet in de laatste plaats is dit te danken aan mijn promotor Prof. Dr. B.L. Feringa oftewel Ben die mij toeliet mijn eigen weg te gaan en waar nodig mijn enthousiasme beteugelde. Met hem samenwerken was een groot avontuur, een belevenis die ik niet snel zal vergeten.

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# CONTENTS

# CHAPTER 1

## INTRODUCTION

### 1.1 *General Aspects*

Oxygen, in its free and bound states, constitutes 46.6% of the mass of the Earth's crust, making it the most abundant element. Selective conversions of hydrocarbons with molecular oxygen is a rewarding goal, that can provide in principle a direct synthesis of valuable oxygenated products such as alcohols, ketones, epoxides, glycols, carboxylic esters, phenols etc.[1]. There are however three major difficulties in synthesizing these compounds:

1) Dioxygen has a triplet ground state and its direct reaction with singlet hydrocarbons is spin-forbidden. Thus, high activation energies are usually required for the initiation step of the addition of dioxygen to hydrocarbons, but once started, oxidation reactions are difficult to control because of their exothermic nature.

2) The primary oxygenated products are often more readily oxidized than the initial hydrocarbons.

3) Often unselective autoxidation may occur to give hydroperoxides which are very reactive compounds and frequently give unwanted side reactions.

In living cells, dioxygen plays a central role. It can either be transported by respiratory enzymes and released at active sites, or activated in enzymatic systems called oxygenases[2]. These oxygenases bring about a great number of selective oxidations such as hydroxylations of hydrocarbons, epoxidations of alkenes, oxidative cleavage etc.. A common feature of all these oxygen carrying and activating systems lies in the fact that transition metals are in most cases present in the active center[3]. These metals, having multiple spin and oxidation states, can readily interact with dioxygen, even to the extent that they form isolable oxygen adducts[4]. In these associations, the metal acts as a

reducing agent and can also polarize the dioxygen bond, facilitating its cleavage. It can also simultaneously bind dioxygen and the substrate and then create the favourable entropic conditions for a selective oxidation to occur.

A wealth of papers has been published during the last decade on transition metal catalyzed oxidation reactions with the aim of mimicking, at least in part, these enzymes. In these papers the ability of numerous transition metal complexes to bind and activate dioxygen or other oxygen donors such as hydrogen peroxide, alkyl hydroperoxides, alkalin hypohalites or iodosylbenzene[5,17] has been described. The recent growth in studies on multimetallic compounds is due to their potential in homogeneous catalysis, the interest in exchange between paramagnetic centers and the role in bioorganic chemistry[6].

There are many multimetal center proteins and enzymes in nature; prominent among these are many with homo and heterodinuclear metal centers[7]. Examples are the active sites in the "blue" multicopper oxidase ceruloplasmin, the dioxygen binding sites in the hemocyanin respiratory proteins and tyrosinase, a mixed function oxidase[8]. An imidazole-bridged copper-zinc pair forms the active site of one type of superoxide dismutase[9].

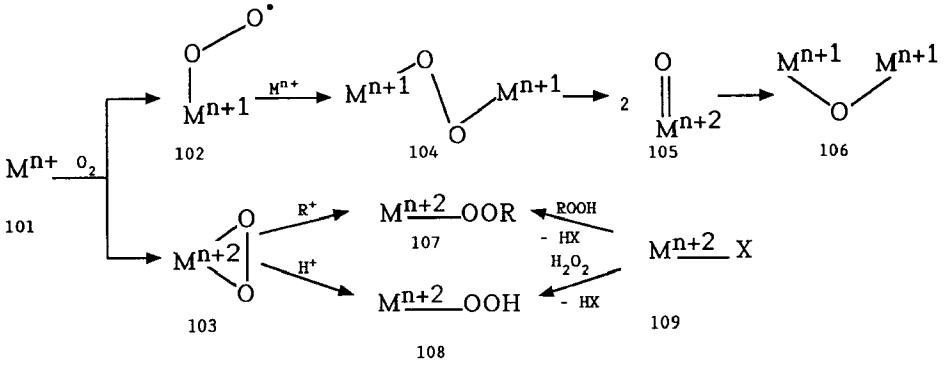
Molecular systems having two redox active centers in close proximity, capable of cooperative interactions, are also of great interest in relation to their potential as catalysts for non-biological substrate oxidation[10].

Considerable effort has thus been directed in recent years towards the synthesis of ligands capable of holding two metal ions, either the same or different, at separations of 2.5-6.0 Å which are controlled by appropriate modification of the molecular topology. Attention to the metal - metal separation and the number, nature and dispositions of the donor atoms allows the study of those physical and chemical properties, which may depend on the dinuclearity of the system[11]. In particular, the possibility is offered to bind and activate small substrate molecules between the metal centers and to investigate structural and physicochemical host - guest relationships.

## 1.2 *Metal-oxygen species*

When dioxygen is allowed to react with transition metal complexes, various metal-oxo species may result, depending on the metal and attached ligands[2,12,13].

In the first place dioxygen can react with the metal center to give a superoxo structure **102** if the metal is a potential one electron donor or a peroxo structure **103** if the metal is a potential two electron donor (scheme 1.1).




*Scheme 1.1: Possible binding modes of metal oxygen species (ligands are omitted for clarity).*

Only iron and cobalt superoxo complexes have been characterized by X-ray analysis[13a]. An example is given in figure 1.1. These superoxo complexes are relevant models for the naturally occurring oxygen carriers hemoglobin and myoglobin. Related superoxo complexes also intervene as primary oxygen adducts in enzymatic cytochrome P450 oxygenases.

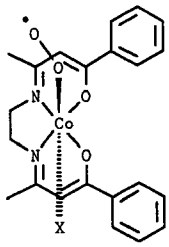
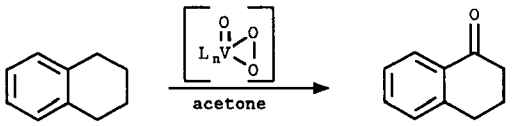



*Figure 1.1: A cobalt superoxo complex (X = pyridine).*

Peroxo complexes are far more numerous than superoxo complexes and have been well characterized for early $d^0$ transition metals (e.g. Ti(IV), V(V), Cr(VI), Mo(VI)) and group VIII complexes[13b] (e.g. Ru(IV), Co(III), Ni(II), Pt(II)). They are important reactive intermediates in catalytic oxidation involving molecular oxygen or hydrogen peroxide as the oxygen source[14]. An example is given in scheme 1.2.




110 111

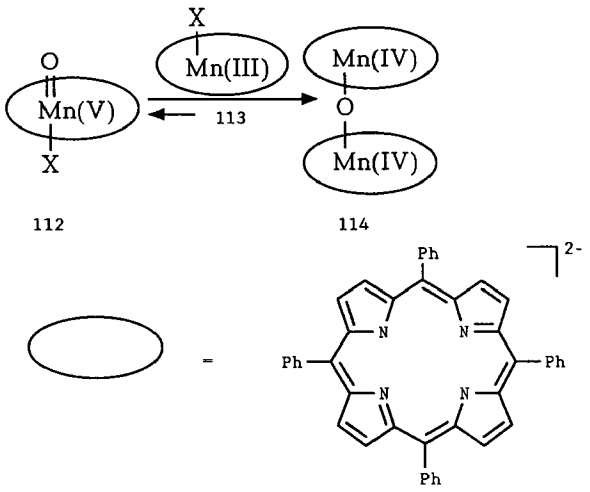
*Scheme 1.2 (L = $H_2O$, $\mu$-oxo)*

In the second place dioxygen can be inserted between two metal ions, between one metal and one carbon atom or between one metal and one hydrogen atom to form $\mu$-peroxo complexes **104**[13c], **107**[13d] or **108**. Bimetallic $\mu$-peroxo complexes can be obtained by reaction of superoxo complex **102** with a second reduced metal complex. Alkylperoxo complexes **107** can be prepared via the insertion of $O_2$ into a metal - carbon bond, from alkylation of metal peroxo complexes or from the reaction of alkyl hydroperoxides with transition metal complexes. Hydroperoxo complexes **108** can be formed from the insertion of $O_2$ into a metal hydride bond, from hydrolysis of a metal-peroxo complex or from the reaction of $H_2O_2$ with a metal salt. These peroxo species are valuable intermediates in the oxidation of saturated hydrocarbons and alkenes by alkyl hydroperoxides, $O_2$ and $H_2O_2$. Some examples will be given in chapter 2.

The $\mu$-peroxo species **104** itself can cleave into oxo-species **105**[13e]. Many oxo metal species have been characterized for the early transition elements, group VIIb and group VIII metals such as Mn, Ru, Os, which are often used as stoichiometric hydrocarbon oxidizing agents. Fe(V)-oxo and Mn(V)-oxo have also recently emerged as plausible reactive intermediates in

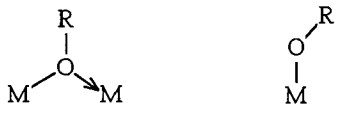
the oxidation of hydrocarbons by monooxygen donor agents catalyzed by iron or manganese porphyrins[15] (see chapter 5).

Metal-oxo species **105** may react with a second metal atom to provide a $\mu$-oxo-species **106**[13f]. Most of these $\mu$-oxo-species are unwanted side products, which lead to inactive catalysts in oxo-transfer reactions. An example[16] is given in scheme 1.3. This dimerization can be suppressed by using bulky ligands attached to the metal centers.




*Scheme 1.3: A porphyrin dimerization.*

If the oxygen source is a monooxygen donor such as iodosylbenzene, tertiar-butyl hydroperoxide or hypochlorite, metal-oxo species **105** can be formed directly but also metal-oxidant complexes **115**[13g] and **116**[13d] (figure 1.2) can be formed as reactive intermediates for oxygen transfer to substrates.




115 116

*Figure 1.2 (R = Cl, PhI, O-t-Bu)*

The existence and stability of the oxygenated forms **102 - 109**, **115** and **116** depends on the nature of the metal and the ligands attached to it.

Metal catalyzed oxidations may conveniently be divided into two types, designated as homolytic and heterolytic[17]. Homolytic oxidations involve free radical intermediates and are catalyzed by transition metals. The hydrocarbon substrate is generally not coordinated to the metal and is oxidized outside the coordination sphere leading to unselective oxidations.

Heterolytic oxidations generally require activation of the substrate by coordination to the metal. They do not involve free radical intermediates and can be highly selective and stereospecific.

In general, the catalytic properties of transition metals for the oxidation of hydrocarbons are strongly governed by the existence and nature of the metal oxygen intermediates.

### 1.3 *Bimetallic oxidation catalysis*

> *"During our research on bimetallic catalysts, it was evident very early that the activities of a metal catalyst for different reactions could be altered to markedly different degrees by the incorporation of a second metallic element into the catalyst."*
>
> J.H. Sinfelt[18], Bimetallic Catalysts, 1983

The advantages of bimetallic (or multimetallic) systems have been established in heterogeneous catalysis for decades but only recently have been recognized in homogeneous catalysis.

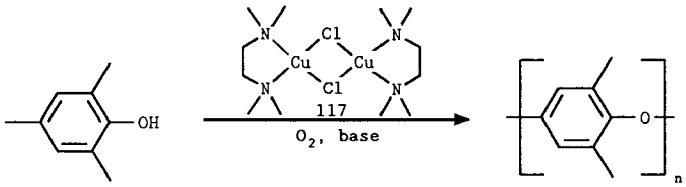
The organization of cations at the molecular level is found in different chemical fields. The interaction between two cations itself has been the subject of intensive study during the last two decades in order to understand the different properties of dinuclear complexes compared to mononuclear analogues. With this fundamental knowledge, several "applications" come in view, such as the mimics of dinuclear metallo enzymes (see chapter 2), the use

of the electron reservoirs as possible catalysts for multi electron processes, the ability to bind two reacting species thereby bringing them in close proximity, etc.

In many cases bimetallic complexes show better catalytic oxidation properties in comparison with monometallic complexes. The effect of a "second" metal in the catalyst complex is proposed to enhance the oxygen binding ability, to assist in oxygen - oxygen bond cleavage or to bind (and activate) both oxidant and substrate on metal ions lying next to each other, thereby favouring oxo-transfer.

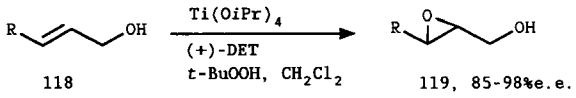
Relatively few of the many synthesized dinuclear complexes[6b,19] have been investigated for their catalytic properties[6], although some beautiful examples of dinuclear metal complexes active in oxidation reactions are known[20-24].

The active catalyst in the oxidative coupling of phenols, using tetra methylenethylenediamine (tmed) as ligand and $CuCl_2$ as source for copper ions, is presumably a dinuclear chloro-bridged complex (**117**) containing one tmed ligand per copper ion[20] (scheme 1.4).




*Scheme 1.4*

Asymmetric epoxidations of allylic alcohols, as discovered by Sharpless and Katsuki[21], can be achieved with a catalyst derived from $Ti(OiPr)_4$ and tartaric esters, giving high enantioselectivities (scheme 1.5).




118 119, 85-98%e.e.

*Scheme 1.5 ((+)-DET = diethyltartrate)*

It is proposed that a dititanium complex **120** is the active catalyst (figure 1.3).

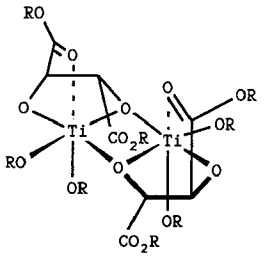
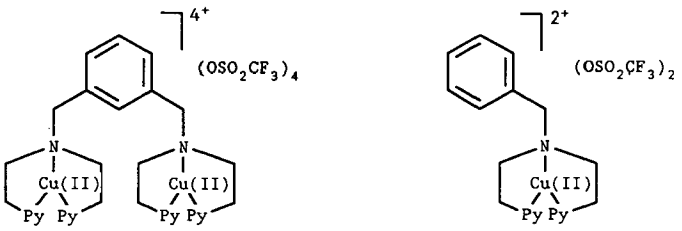



*Figure 1.3: Proposed structure for the active catalyst in the epoxidation reaction of allylic alcohols.*

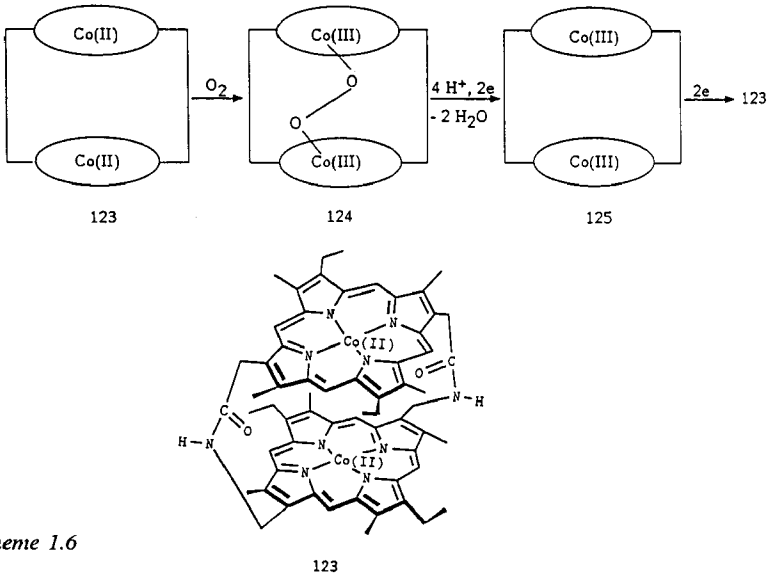
Valentine and co-workers[22] reported the epoxidation of olefins using iodosylbenzene and some dinuclear copper(II) complexes (figure 1.4), which were considerably better catalysts than their mononuclear analogs.




121 122

*Figure 1.4: Complex **121** is a nine times more active catalyst in the epoxidation of styrene than **122**.*

Collman and co-workers[23] described the synthesis of bis-cobalt(II) complex **123** of a face to face diporphyrin ligand capable of the four electron reduction of oxygen to water (scheme 1.6).




*Scheme 1.6*

Although a large number of dinuclear $\mu$-oxo complexes of Mn, Fe, Mo, Cr, etc. have been described[24], few of them have been investigated with regard to oxo-transfer reactions to organic substrates. In most cases they are believed to be unreactive intermediates compared to their mononuclear oxo analogs. An example is given in scheme 1.3 where the dimerisation leads to an unreactive complex[16]. These dimerisation reactions, which can lead to unreactive catalysts, can be avoided by appropriate choices of the ligand system. Increasing the steric hindrance of the tetraphenylporphyrin (TPP) ring in **112** by replacement of the phenyl substituents by *o*-dibromophenyl substituents prevents this dimerization[25] (see also section 5.2).

## 1.4 *Aims and scope of this thesis*

The purpose of this investigation was to develop new bimetallic catalysts which are capable of accomplishing specific oxygen transfer from oxidants such as molecular oxygen, sodium hypochlorite, alkyl hydroperoxides, etc. to organic substrates. Therefore, the synthesis, structural characterization and reactivity of novel bimetallic copper and nickel complexes are described in this thesis.

The results discussed in this thesis can be divided into two sections. The chapters 2, 3 and 4 deal with dinuclear Cu(I) and Cu(II) complexes and their reactivity in oxidation reactions using molecular dioxygen as the oxidant. Chapters 5 and 6 deal with the synthesis of chiral dinuclear Ni(II) species and their catalytic activity in epoxidation reactions of alkenes.

Chapter 2 describes a synthetic mimic for the active site of the binuclear copper protein tyrosinase; a monooxygenase.

In Chapter 3 a mechanistic investigation is presented of novel hydroxylation and demethoxylation reactions found for these dinuclear complexes. A mechanistic rational is given.

Chapter 4 deals with the synthesis and reactivity of a dinuclear *p*-hydroquinone copper(II) complex, designed to function as an oxidation catalyst with a built in electron shunt. The results of studies on the catalytic activity in the oxidations of $\alpha$-hydroxyketones and hydroquinones to diketones and quinones, respectively, are given.

In chapter 5 the synthesis of several (S)-proline-derived chiral bis copper(II) and bis nickel(II) complexes are described. The chiral bis copper(II) complexes were investigated in kinetic resolution experiments of $\alpha$-hydroxyketones. The chiral bis nickel(II) complexes were investigated with respect to their ability to catalyze the epoxidation of alkenes using tertiar butyl hydroperoxide or sodium hypochlorite as the oxidant.

In chapter 6 chiral dinuclear Ni(II) catalysts are described which are based on new multidentate ligands that are designed to reinforce binding ability and enhance diastereomeric selection.

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# CHAPTER 2

## A SYNTHETIC MODEL FOR THE ACTIVE SITE OF DINUCLEAR COPPER PROTEINS

### 2.1 *Introduction*

In this chapter a new model system that can mimic the active site of certain enzymes that bind or activate molecular oxygen will be described. These enzymes have in common that the active site contains a pair of copper ions, coordinated by nitrogen containing ligands, in most cases derived from histidine residues from the protein. Currently much effort is being devoted to develop useful catalytic systems, based on structural and mechanistic principles of these enzymes, for mild and selective oxidations with the aid of molecular oxygen. It is also of great interest to elucidate the factors that determine the (reversible) binding and activation of dioxygen in these natural oxygen transport, mono-, and dioxygenase systems.

### 2.2 *Copper Enzymes*

In nature various enzymes are found which contain an active center in which a dinuclear copper unit is present[1]. Among these proteins hemocyanin[2], tyrosinase[3] and dopamine-ß-hydroxylase[3,4] have been investigated to the greatest extent. The precise function of the dinuclear copper center in these particular enzymes is different, but in all cases binding and/or activation of molecular oxygen is concerned[5].

*Hemocyanin*

Hemocyanin functions as a dioxygen carrier protein in the hemolymph of several species of the phyla Mollusca and Arthropoda[6]. A recent X-ray

structural study on deoxyhemocyanin[7] shows that three imidazole ligands from histidine units in the protein bind to Cu(I) ions to form a dinuclear metal center (Cu · · · Cu = 3.4-3.7 Å). The binding site for copper is rather distorted with each Cu(I) ion having two strongly coordinated imidazole ligands with a third imidazole ligand bound more weakly. No protein-derived ligand serves as a bridging group in deoxyhemocyanin and the detection of a "small" group such as $OH^-$ or $H_2O$ as a bridging ligand would seem to be precluded by the 3.2 Å resolution of the X-ray structure. Upon reaction with molecular oxygen a stoichiometry of Cu : $O_2$ of 2 : 1 is found[8] (figure 2.1).

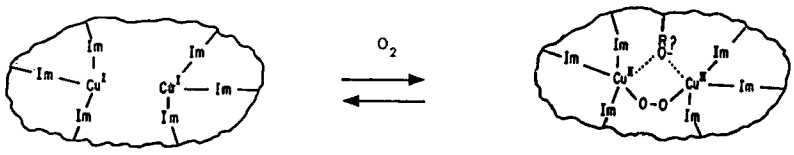



*Figure 2.1: Proposed structure for the active site of the dioxygen carrier protein hemocyanin in the deoxy and oxy states[7,14] (Im = Imidazole)*

The binding of oxygen is supposed to occur via an inner sphere redox reaction between the two Cu(I) centers and dioxygen giving a peroxo dicopper(II) ($Cu_2O_2^{2+}$) species[9]. In this species the Cu(II) ions are bridged in a cis $\mu$-1,2 fashion by dioxygen. In the oxy form a change in coordination is found which results in four or five coordinated Cu(II) ions separated from each other by 3.6(±0.05) Å as determined by EXAFS[10] studies. Due to the strong antiferromagnetic coupling of the Cu(II) centers a bridging ligand was proposed[11]. This bridging ligand is often referred to as the "endogenous" bridge, but since a $RO^-$ donor ligand, derived from protein residues such as serine or tyrosine appears to be ruled out by the crystal structure of deoxyhemocyanin and the sequence analysis studies, $OH^-$ and $H_2O$ are the most likely candidates[11].

*Tyrosinase*

Tyrosinase is an enzyme widely found in microorganisms, plants and animals[12]. It belongs to the class of the monooxygenases, therefore it incorporates one O atom, from $O_2$, into a substrate whereas the other oxygen atom is reduced to water[13]. It specifically catalyses the ortho-hydroxylation of phenols to *o*-diphenols and the further oxidation of these products to *o*-quinones[14]. Although its active site is less well defined as compared to the active site in hemocyanin, there are many chemical and spectroscopic similarities. The Cu : $O_2$ stoichiometry is the same and resonance Raman and UV-Vis spectra of both oxy forms of hemocyanin and tyrosinase are comparable. Both produce a distinct $O_2^{2-} \rightarrow$ Cu(II) charge transfer band at 350 nm indicating a peroxide bound in a $\mu$-1,2 geometry in both enzymes[15]. The ligand displacement of peroxide from the active site by $N_3^-$ and l-mimozine (organic substrate inhibitor) is much faster for oxytyrosinase than for oxyhemocyanin[16]. Thus oxytyrosinase has a greater accessibility to exogenous ligands. It is proposed that in the case of tyrosinase, after $O_2$ complexation, phenol coordinates to one of the Cu ions thereby rearranging the coordination sphere of that ion. This results in a polarization of the $\mu$-1,2-peroxo bridge. This O - O bond polarization activates the attack of peroxide on the substrate, resulting in ortho hydroxylation to catechol. In a subsequent step, the oxidation of the catechol by the two Cu(II) ions in the active site to an *o*-quinone and two Cu(I) ions completes the catalytic cycle[17].

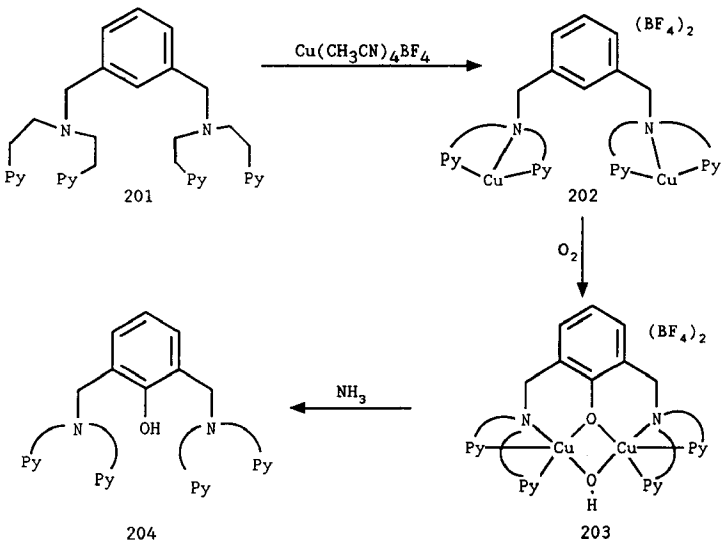
*Dopamine-ß-hydroxylase*

Dopamine-ß-hydroxylase also belongs to the monooxygenase family, although in this case a cofactor, usually ascorbate, is required. It catalyses the last step in the biosynthesis of the neurotransmitter noradrenaline via the hydroxylation of dopamine[4,18]. It contains four magnetically isolated Cu(II) ions per tetramer unit. EXAFS studies suggest that there are at least three coordinated imidazole ligands per Cu(II) ion in the oxy form[19]. The stoichiometry of the overall reaction requires one molecule of dioxygen, two

electrons and one substrate molecule. All these observations and the analogy with tyrosinase suggest that a dinuclear copper containing active site would be reasonable. However this is inconsistent with a "normal" single Cu(II) EPR signal, observed for dopamine-ß-hydroxylase[20], consistent with the characteristics of mononuclear Cu(II) complexes.

### 2.3 *Monooxygenase model systems*

In order to mimic the active site of monooxygenases, as described in the previous section, several attempts have been made using relative "simple" metal coordination complexes[21]. To date the best model system has been described by Karlin and co-workers[21b]. In an attempt to imitate the active site of hemocyanin they found an unusual copper(I) promoted hydroxylation reaction with molecular oxygen of the 1,3-disubstituted phenyl group in the dinucleating ligand *m*-XYL-py-2 (**201**) (py-2 = the tridentate ligand bis(2-(2-pyridyl)ethyl)amine (scheme 2.1). Ligand **201** is able to bind two Cu(I) ions to




*Scheme 2.1 (Py = 2-pyridyl)*

form the dinuclear complex **202**. Each Cu(I) ion is three coordinated, with ligation from two pyridine and one tertiary amine donor group with a Cu(I) - Cu(I) separation of 8.940 Å. This dinuclear Cu(I) complex **202** reacts with stoichiometric amounts of molecular oxygen to form a dioxygen bridge between the two copper centers, resulting in a peroxo dicopper(II) species ($Cu_2O_2^{2+}$).

The exact mode of $O_2$ binding is not known until now. Karlin and co-workers isolated a trans $\mu$-1,2-peroxide adduct (**205**) of a mononuclear Cu(I) complex of tris[(2-pyridyl)methyl]amine (figure 2.2) demonstrating that a $Cu_2O_2^{2+}$ species really can exist[22]. Kitajima and co-workers recently isolated and characterized structure **206** with a $\mu$-$\eta^2$:$\eta^2$ coordinated peroxide ion bridging to two Cu(HB(3,5-iPR$_2$Pz)$_3$) ( HB(3,5-iPR$_2$Pz)$_3$ = hydrotris(3,5-isopropyl-1-pyrazolyl)borate ) molecules[23] having a Cu - Cu separation of 3.560(3) Å. The Cu - Cu distance is very consistent with the estimated values for oxyhemocyanin (3.58-3.66 Å)[10] and oxytyrosinase (3.63 Å)[24] as determined by EXAFS analyzes.

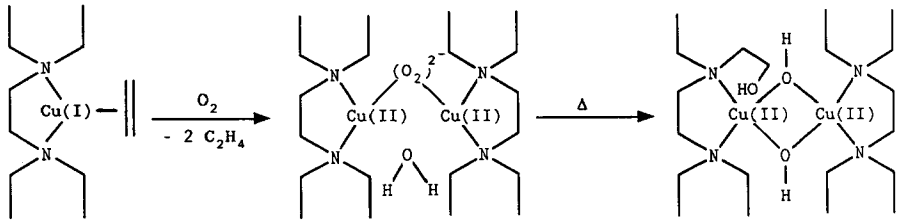

*Figure 2.2: Different binding modes of dioxygen towards Cu(I) complexes*

The dioxygen binding to complex **202** is reversible at -80°C in $CH_2Cl_2$. When the temperature of the intense purple solution of the dioxygen complex of **202** in $CH_2Cl_2$ is allowed to rise, the colour vanishes and irreversibly a green-coloured solution, consisting of complex **203**, is formed. Surprisingly hydroxylation of the *m*-xylyl bridge in **202** had taken place. In complex **203** the Cu(II) ions are bridged by a phenoxy and a hydroxy ligand. Control experiments, using $^{18}O_2$, showed that both oxygen atoms were incorporated into complex **203**, excluding any hydrolytic pathway. In this way **202** mimicks, tyrosinase

related, monooxygenase activity. X-ray analysis of the oxygenated product **203** showed a nearly planar $Cu_2O_2$ unit having a geometry of an undistorted tetragonal pyramid around each Cu(II) atom with a Cu - Cu separation of 3.082(3) Å. Release of the Cu(II) ions by an ammonia extraction procedure gave the corresponding phenol **204** in 90% overall yield from **202**. Although, since then, extensive work has been performed to elucidate a mechanistic pathway for this reaction, no well defined mechanism can be given at present (see also chapter 3). When small changes where made in ligand **201**, e.g. replacement of the pyridine by pyrazole, as described by Sorrell[25a], no hydroxylation of the ligand was seen. Even mixed pyrazole-pyridine ligands showed no oxygen incorporation[25b].

At the time we started this investigation and discovered an arene hydroxylation[26], a second very similar hydroxylation reaction was found by Casella and co-workers[27]. They synthesized dinuclear Cu(I) complexes, derived from benzene-1,3-dicarboxaldehyde and two molecules of histamine or histidine derivatives. Upon reaction with dioxygen they found oxygen insertions in most cases. In these cases a competition between aromatic hydroxylation and simple Cu(I) oxidation was observed. In acidic media an enhancement of the hydroxylation reaction was found, indicating the involvement of a protonated form of the dicopper bound dioxygen. In connection with this issue of proton assistance one other complex, described by Thompson[28], deserves comment. N,N,N$^1$,N$^1$-tetraethylethylene diamine and ethylene form a stable copper(I) adduct **207** that reacts with dioxygen at low temperature in a methanol/water mixture to form a dinuclear complex **208** in which the Cu(II) ions are bridged by peroxide and water (scheme 2.2). Upon standing at room temperature a hydroxylation at a terminal ethylene carbon atom takes place to form complex **209**.

In a model system described by van Koten and co-workers[29] an aromatic hydroxylation involving the conversion of a Cu(I) - C bond into a Cu(I) - OC bond was found, which is interesting in view of the reactivity of metal-carbon bonds towards oxygenating agents.




207 208 209

*Scheme 2.2*

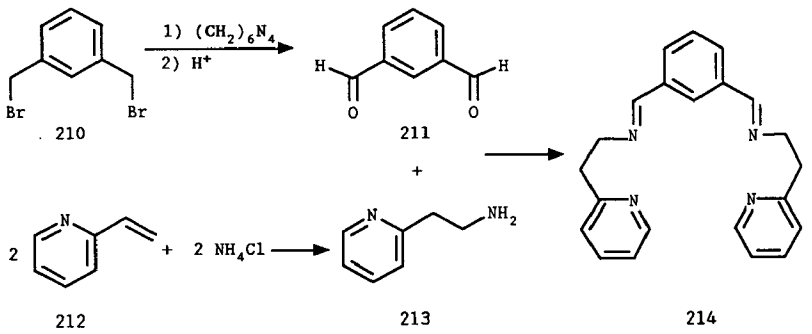
Although Cu-promoted hydroxylations by now have good precedent, little is known and understood about the factors that determine the hydroxylation reaction. Also no model systems have been reported yet that can serve as efficient catalysts in hydroxylation reactions as performed by tyrosinase.

In order to develop new bimetallic catalysts for homogeneous oxidations, these kind of dicopper systems looked very promising. Therefore we decided to investigate a ligand system which contains two bidentate complexing moieties and which is easily prepared. We expected that this ligand would be capable of binding two Cu(I) ions and would bring them in close proximity, leaving enough unoccupied coordination sites for the activation of dioxygen as well as a substrate molecule. Our final goal was to develop complexes, based on dicopper chemistry, which would be capable of catalyzing the oxidation of external substrates.

In the following sections and chapter 3 and 4 new model systems and catalysts are described which mimic, at least in part, the copper dependent enzyme tyrosinase. Also a mechanistic investigation was executed and an interpretation of the results will be given.

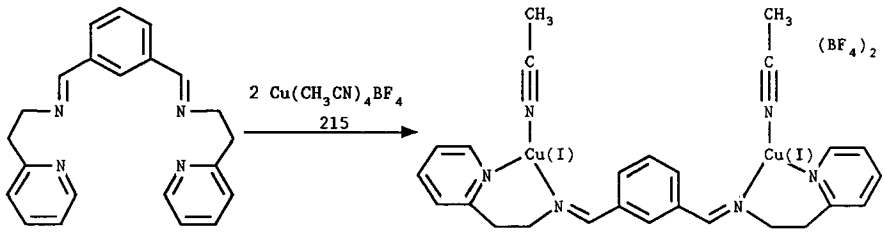
## 2.4 *Synthesis of a dinuclear Cu(I) complex*

With the aim of development of new bimetallic oxidation catalysts we synthesized the previously unknown ligand 1,3-bis[N-(2-(2-pyridyl)ethyl) formimidoyl]benzene (**214**). This was prepared in a three step synthesis starting from $\alpha,\alpha'$-dibromo-*m*-xylene (**210**) and 2-vinylpyridine (**212**) (scheme 2.3). In the first step **210** is oxidized in a Sommelet reaction using hexamethylenetetramine to provide isophthalic aldehyde **211** in 50% yield as white crystalline material[30]. Although several other methods are available for the preparation of this aldehyde, e.g. hydrolysis of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*m*-xylene with concentrated $H_2SO_4$[31], the present route allows rapid and facile preparation of **211**. Then 2-vinylpyridine (**212**) was converted to 2-(2-pyridyl)ethylamine (**213**) by a Michael type reaction with ammonium chloride using a literature procedure[32]. In the last step two equivalents of amine **213** were condensed with dialdehyde **211** to provide the tetradentate ligand 1,3-bis[N-(2-(2-pyridyl)ethyl)formimidoyl]benzene (**214**) as a colourless oil in 90% yield. The formation of **214** could easily be followed in the $^1$H NMR spectrum where the aldehyde protons of **211** moved about 2 ppm upfield in the imine **214**. In **214** two bidentate 2-(2-pyridyl)ethyl imine units are separated by a *m*-xylyl bridge.




*Scheme 2.3*

This ligand was made with the intention of providing the capacity to bind two Cu(I) ions, thereby forming a dinuclear Cu(I) complex. In line with this expectation we found that when **214** was added to a suspension of $Cu(CH_3CN)_4BF_4$[33] (**215**) in THF, under a nitrogen atmosphere, an orange-yellow powder was isolated in 85% yield (scheme 2.4). After recrystallization from $CH_2Cl_2/CH_3OH$ (10 : 1) yellow needles were obtained. Elemental analysis of the product revealed a copper to ligand ratio of 2 : 1 indicating that two Cu(I) ions are bound to the ligand. The Cu : N ratio (1 : 3) indicated a three coordination around each Cu(I) atom. The product is quite stable to air in the solid state but reacts readily with dioxygen when it is brought into solution. In order to establish unequivocally the structure of the product an X-ray analysis was undertaken. The ligand **214** had formed a dinuclear Cu(I) complex **216** with a trigonal coordination sphere around each Cu(I) atom (vide infra).




214 216

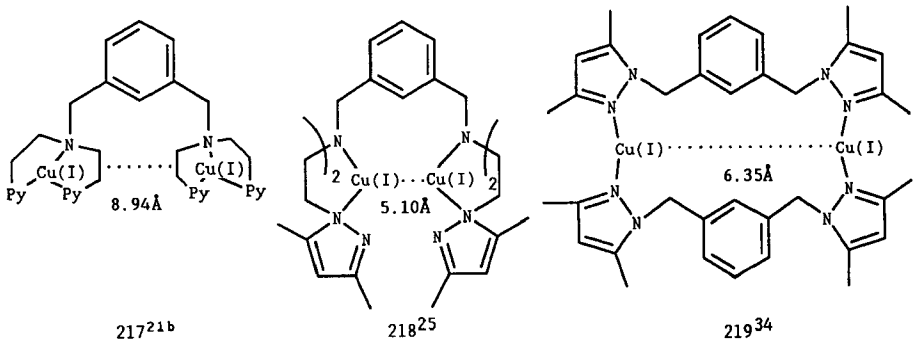
*Scheme 2.4*

## 2.5 *Copper(I) coordination and crystal and molecular structure of 216*

The electronic configuration of Cu(I), $3d^{10}$, involves a filled 3d shell and hence spherical symmetry for the Cu(I) ion. The stereochemistry of Cu(I) in its molecular complexes is dominated by four coordination. A few three and two-coordinated complexes are known. Very few five coordinated complexes exist and six coordination is unknown. When using identical ligands, four

coordinated copper(I) complexes generally are tetrahedral, whereas three coordinated Cu(I) has a trigonal planar arrangement thereby minimizing steric effects. For macrocyclic type chelate ligands distortion from trigonality around Cu(I) occurs and the coordination of the ligand is best described as T-shaped[34].

Most dinuclear Cu(I) complexes are bridged by one or two heteroatoms (e.g. I, Br ,OMe ,OPh) giving trigonal, tetrahedral and mixed trigonal, tetrahedral stereochemistry. In the case of dinuclear Cu(I) complexes where the bridging unit consists of an organic chain the ions may be two, three or four coordinated[21,25,35]. In these systems the Cu(I) ions can be so far apart that the compounds may be considered as two connected mononuclear copper complexes. Some examples of such complexes, with the Cu(I) - Cu(I) distances, are given in figure 2.3.




217[21b] 218[25] 219[34]

*Figure 2.3: Some examples of dinuclear Cu(I) complexes (Py = 2-pyridyl)*

In order to obtain crystals of **216** which were suitable for an X-ray analysis, small needles of **216** were allowed to stand for a long period in a $CH_2Cl_2/CH_3OH$ (10 : 1) solution; suitable large yellow needles were eventually obtained.

Complex **216** crystallizes in the triclinic space group $P\bar{1}$ with two crystallographically independent molecules in the unit cell. Each unit cell contained two solvate molecules $CH_2Cl_2$ (as was also determined by elemental

analysis). The cell dimensions are a = 10.003(4), b = 10.979(2) and c = 29.763(5) Å. The final refinement (R index) was 0.076. The molecular structure is depicted in figure 2.4 and some selected data are given in table 2.1.

Each Cu(I) ion is coordinated to three nitrogen donor atoms, two of which originate from the pyridylethylimine moiety and one from acetonitrile. The $N_{imine}$ - Cu - $N_{nitril}$ angles [143.9(5)° and 149.4(5)°] are larger then the $N_{pyr}$ - Cu - $N_{nitril}$ angles [109.9(4)° and 108.0(5)°] probably due to some steric interaction of the $CH_3CN$ coordinating ligand with the bridging xylene moiety. The Cu(I) ions are well separated with a Cu(1) - Cu(2) distance of 4.952(2) Å, which is however relatively short compared to complexes **217** and **218**. Distortion from planarity occurs mainly at only one of the Cu(I) sites with Cu(1) 0.181 Å out of the N(1), N(2), N(6) plane and Cu(2) only 0.045 Å out of the N(3), N(4), N(5) plane. The larger deviation at Cu(1) might be caused by interaction with the pyridine nitrogen of a second dication as suggested by the structure analysis. The Cu - N bond lengths fall into the range generally found for three coordinated complexes except for the Cu - $N_{pyr}$ bond lengths [2.066(10), 2.086(11) Å], which are unexpectedly large when compared to the bond lengths [1.88-2.02 Å] usually found between Cu(I) and N-heterocyclic donors in three coordinated complexes[21a,b,25a]. This is probably due to more steric interaction between the bidentate and monodentate ligands compared to the tridentate ligands described in literature.

Only a limited number of three coordinated Cu(I) complexes containing unsaturated nitrogen ligands have been characterized[36]. Complex **216** is the first three coordinated dinuclear Cu(I) species in which one bidentate and one monodentate ligand are coordinated to each Cu(I) ion.

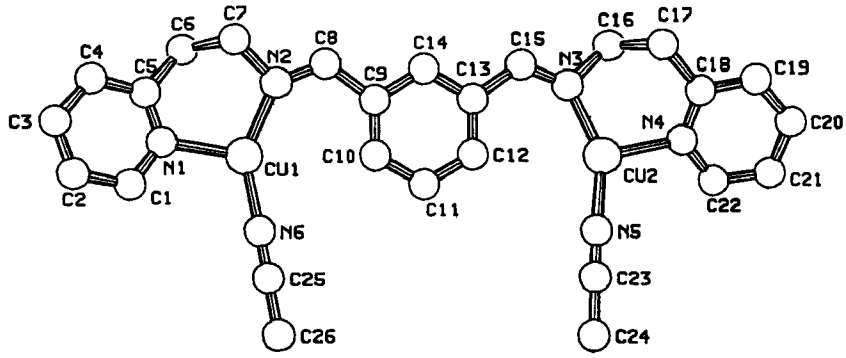



*Figure 2.4: Molecular structure and adopted numbering scheme of 216 (only the cationic part is shown for clarity).*

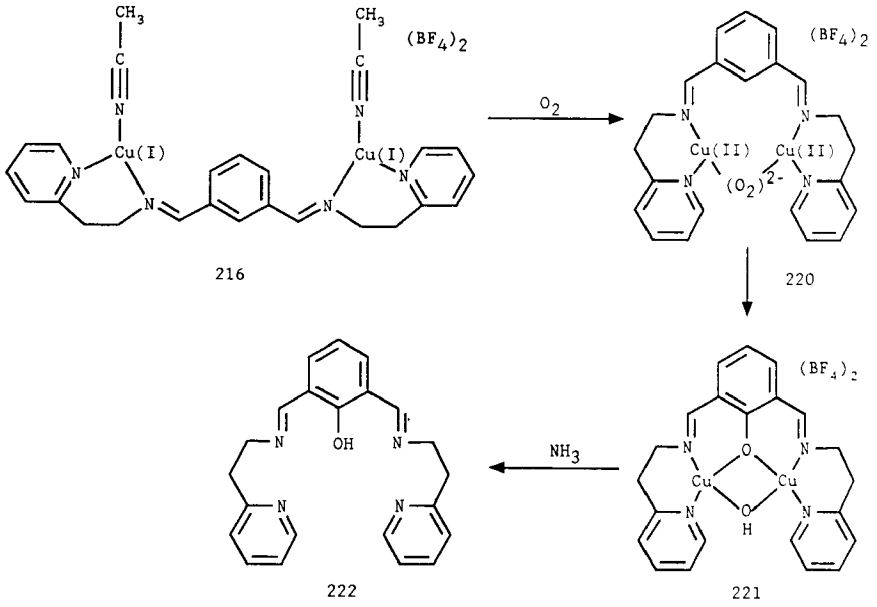
*Table 2.1: Selected interatomic distances (Å) and angles (deg) for 216*

| | | | |
|---|---|---|---|
| N(1) - Cu(1) | 2.066(10) | N(1) - Cu(1) - N(2) | 103.3(4) |
| N(2) - Cu(1) | 1.978(11) | N(1) - Cu(1) - N(2) | 109.9(4) |
| N(6) - Cu(1) | 1.951(12) | N(2) - Cu(1) - N(6) | 143.9(5) |
| N(3) - Cu(2) | 1.955(11) | N(3) - Cu(2) - N(4) | 102.3(5) |
| N(4) - Cu(2) | 2.086(11) | N(3) - Cu(2) - N(5) | 149.4(5) |
| N(5) - Cu(2) | 1.895(12) | N(4) - Cu(2) - N(5) | 108.0(5) |
| Cu(1)· · · Cu(2) | 4.952(2) | | |

### 2.6 *Oxidation of 216 with dioxygen*

Whereas **216** is air stable in its crystalline state, solutions of this complex in $CH_2Cl_2$, $CH_3OH$, $CH_3CN$ or mixtures of these solvents undergo a rapid colour change from yellow to dark green. Manometric experiments showed that a stoichiometric reaction between **216** and dioxygen takes place (scheme 2.5). In a few minutes already 80% of the theoretical amount dioxygen (based on starting material) was consumed, indicating a very fast oxidation reaction. After one hour oxygen uptake ceased completely. Isolation of the oxidation product after one hour, by crystallization of the green material from an $C_2H_5OH/H_2O$ mixture gave a dark green crystalline complex (65%

yield). Elemental analysis of this complex showed a copper to ligand ratio of 2 : 1 and a copper to nitrogen ratio of 1 : 2. IR analysis showed a large and broad absorption in the 3500 $cm^{-1}$ region, indicating a hydrogen-heteroatom bond, probably OH. In order to characterize this complex to the greatest extent an X-ray analysis was undertaken (vide infra). The X-ray analysis of this complex revealed incorporation of two oxygen atoms into the complex **216**, with one of the oxygen atoms formally inserted into the aryl - hydrogen bond of the *m*-xylyl bridge, whereas the other oxygen atom is incorporated into a hydroxy bridge.




*Scheme 2.5*

We suppose that, in accordance with the work described in section 2.3 these oxygen atoms originate from molecular oxygen. Presumably molecular oxygen will bind to the two Cu(I) ions forming a $\mu$-1,2, $\mu$-1,1 or $\mu$-$\eta^2$:$\eta^2$ peroxide intermediate **220** (scheme 2.5). Attempts to perform this oxygenation reaction at low temperatures failed to give the deep purple coloured peroxo dicopper(II) intermediate **220**, as seen for related species by other groups[23,37].

Instead only a colour change from yellow to dark green (formation of **221**) (at -40°C) or no colour change at all (at -80°C) could be observed. The oxygen binding must be preceded by a rotation around both aryl-imine carbon - carbon bonds in order to bring the two Cu(I) ions in close proximity, allowing the formation of the peroxo dinuclear Cu(II) complex **220**. This also explains why in the solid state **216** is quite stable to air: the Cu(I) ions are too far apart to be bridged by dioxygen. In the next step **220** collapses to the final product **221**.

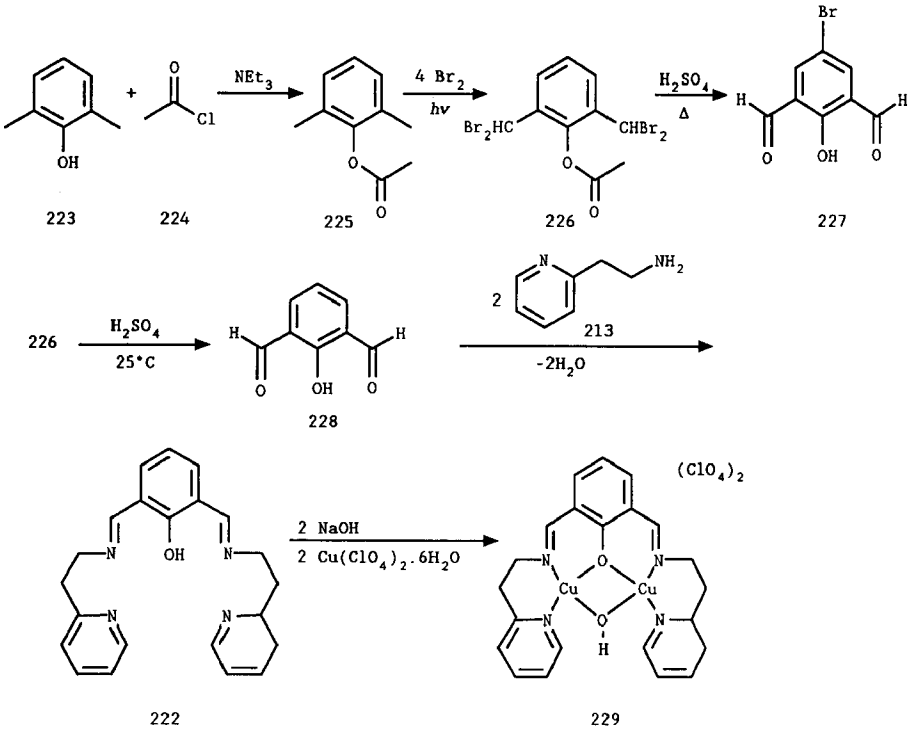
Complex **221** was examined electrochemically by using cyclic voltammetric measurements. In acetonitrile, under a nitrogen atmosphere, no reversible oxidation-reduction sequence at the copper centers was seen. One irreversible reduction at -0.49 V (vs. $H_2/H^+$) was found. This is probably caused by a reduction of the copper(II) centers to metallic copper or to unstable Cu(I) species which disproportionate into Cu(0) and Cu(II).

EPR studies, performed in DMSO or $CH_3OH$ gave no signals in the temperature range -80°C - +40°C, thereby indicating that no unpaired electrons can be detected.

The phenolic ligand **222** could be obtained from **221** in 90% yield by an ammonia extraction procedure as described by Karlin[21b] for a related complex. Ligand **222** was different from the starting ligand **214** as could easily be seen in the $^1H$ NMR spectrum (disappearance of the singlet at 7.87 ppm of the $H_2$ of the aromatic H-atoms) and the mass spectrum ($M^+$ at 358).

For a definitive confirmation of the remarkable arene hydroxylation and in order to have an alternative synthesis of **221**, the ligand **222** was also prepared independently starting from 2,6-dimethylphenol (**223**) as outlined in scheme 2.6.

In the first step 2,6-dimethylphenol (**223**) is converted into its acetic acid ester by reaction with acetylchloride and triethylamine. It is necessary to protect the phenolic group because in the next step **225** is converted into its




*Scheme 2.6*

tetrabromo analog **226** by a radical bromination (70% yield). If the phenol was unprotected bromination occurred at the aromatic ring, as is normal for brominations performed with unprotected phenols[38]. Hydrolysis of **226** with concentrated $H_2SO_4$ at room temperature gave the corresponding 1-hydroxybenzene-2,6-dicarboxaldehyde **228** as white crystalline material in 40% yield. When during this hydrolysis procedure the temperature was raised to 60°C a 100% *p*-brominated product **227** was isolated. To suppress this bromination reaction during hydrolysis the optimal selectivity versus yield was achieved with a 16 h. reaction time at room temperature. Only limited use has been made of the conversion of xylenes into phthalic dialdehydes using the tetra-bromination, followed by hydrolysis sequence. The formation of isophthalic aldehyde from *m*-xylene has been reported[31]. In our hands this proved to be

an excellent procedure to prepare various isophthalic aldehydes. Several examples will follow in the next chapters. Dialdehyde **228** was easily converted to the diimine ligand **222** by condensation with two equivalents of 2-(2-pyridyl)ethylamine **213** in $CH_2Cl_2$. The direct hydroxylation of **216** followed by ammonia extraction and the straightforward synthesis of **222** according to scheme 2.6 gave identical products in all respects.

The perchlorate analog of **221** was also prepared independently by reaction of **222** with two equivalents of NaOH and $Cu(ClO_4)_2 \cdot 6H_2O$ in refluxing methanol. This procedure gave the dark green crystalline complex **229** in 45% yield. Elemental analysis of **229** is in accord with the proposed structure, as depicted in scheme 2.6.

### 2.7 *Copper(II) coordination and X-ray structure of 221*

The Cu(II) ion, having a $d^9$ configuration, is the most common oxidation state of copper except for Cu(0). Complexes containing Cu(I) are often readily oxidized to Cu(II) and furthermore Cu(I) can undergo disproportionation into Cu(II) and Cu(0). Like the other first row transition metal(II) cations, Cu(II) readily forms coordination complexes involving mainly the coordination numbers four, five and six. The geometries range from tetrahedral and square coplanar for four coordinate, square pyramidal and trigonal bipyramidal for five coordinate and octahedral for six coordinate complexes. A seemingly infinite variety of distortions from these geometries are observed for Cu(II) complexes[39].

Many dinuclear Cu(II) complexes have been prepared for three reasons. (1) They are readily prepared by normal methods applicable for mononuclear complexes. (2) They provide simple models for the study of the magnetic interaction of the two unpaired d electrons and (3) they are useful models for biological systems containing copper ions as described previously. A number of these dinuclear Cu(II) complexes are prepared starting from the readily available building block 1-hydroxy-4-methylbenzene-2,6-

dicarboxaldehyde[40]. Condensation with two equivalents of diamine gives the pentadentate acyclic diazediamine N,N,N,N,O ligand system which is capable of forming phenoxy and hydroxy bridged dinuclear Cu(II) complexes. Some examples are given in figure 2.5.

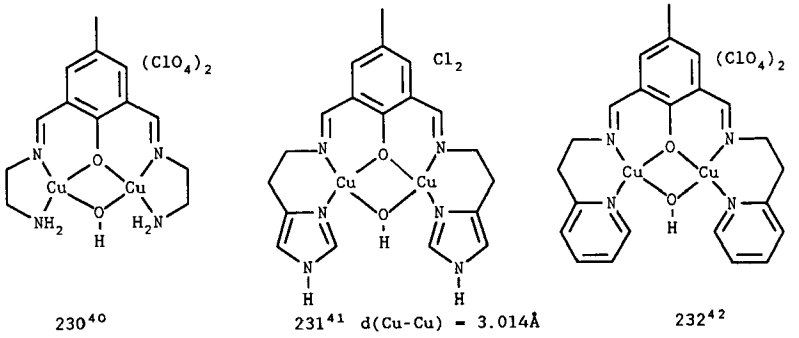



*Figure 2.5: Some examples of hydroxy-phenoxy bridged dinuclear Cu(II) complexes*

In order to establish the proposed structure of **221** an X-ray analysis was undertaken. Crystallization of **221** from an $C_2H_5OH/H_2O$ mixture gave **221** as dark green, diamond shaped crystals suitable for X-ray analysis. The complex crystallizes in the triclinic space group $P\bar{1}$ with unit cell dimensions of a = 9.323(4), b = 10.499(2) and c = 14.179(4) Å. Each unit cell contained one molecule of **221**. Some disorder was found in the ethylene bridge (C(21),C(22)) of the molecule; 50% of C(21) lies above and 50% lies under the $Cu_2O_2$ plane. For C(22) the site occupation is vice versa to C(21). In a difference Fourier map, without C(21) and C(22), four peaks with nearly the same electron density were located on positions with reasonable geometry. Carbon atoms C(211), C(212), C(221) and C(222) introduced with a site occupation factor of 0.5 in these positions refined satisfactory. The structure was solved to an R index of 0.044. The geometry around each Cu(II) in **221** is slightly distorted square planar with a Cu(II) - Cu(II) separation of 2.990(2) Å. The latter is typical for dinuclear copper(II) complexes containing two one-atom bridging ligands[44] (see Cu - Cu distances in figure 2.5) and is considerable shorter than the Cu - Cu distance in oxyhemocyanin. The $Cu_2O_2$ unit

deviates from planarity with an O(1) - Cu(1) - O(2) - Cu(2) torsion angle of 9.3(2)°. The molecular structure is depicted in figure 2.6 and some selected bond distances and angles are given in table 2.2.

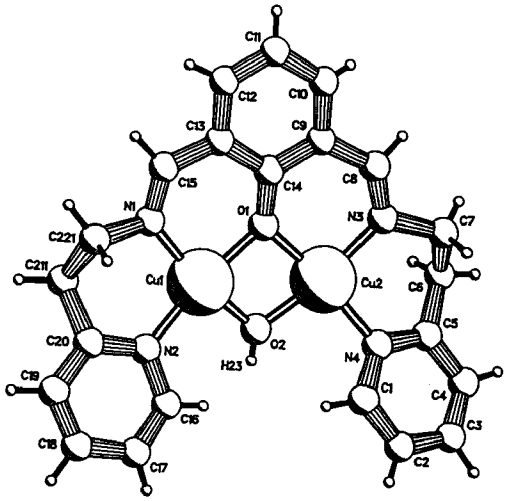



*Figure 2.6: Molecular structure and adopted numbering scheme of 221 (only the cationic part is shown for clarity).*

*Table 2.2: Selected interatomic distances (Å) and angles (deg) for 221*

| | | | |
|---|---|---|---|
| Cu(1) - N(1) | 1.933(6) | N(1) - Cu(1) - N(2) | 96.4(2) |
| Cu(1) - N(2) | 1.996(5) | N(1) - Cu(1) - O(1) | 90.7(2) |
| Cu(1) - O(1) | 1.968(4) | N(2) - Cu(1) - O(1) | 171.1(2) |
| Cu(1) - O(2) | 1.909(4) | N(2) - Cu(1) - O(2) | 95.3(2) |
| Cu(2) - N(3) | 1.939(5) | N(1) - Cu(1) - O(2) | 166.1(2) |
| Cu(2) - N(4) | 1.991(5) | O(1) - Cu(1) - O(2) | 78.3(2) |
| Cu(2) - O(1) | 1.967(4) | N(3) - Cu(2) - N(4) | 96.5(2) |
| Cu(2) - O(2) | 1.911(4) | N(3) - Cu(2) - O(1) | 91.8(2) |
| Cu(1) · · · Cu(2) | 2.990(2) | N(4) - Cu(2) - O(1) | 169.9(2) |
| | | N(4) - Cu(2) - O(2) | 93.6(2) |
| | | O(1) - Cu(2) - O(2) | 78.3(2) |
| | | N(3) - Cu(2) - O(2) | 169.9(2) |

## 2.8 *Concluding remarks*

The insertion reaction of molecular oxygen into an aryl C - H bond with the aid of two Cu(I) centers as described in this chapter, might have consequences for the design of new ligand systems for dinuclear copper enzyme models that mimic tyrosinase and hemocyanin. Considering earlier results of Karlin and co-workers which led to the conclusion that small electronic effects are crucial in determining whether or not this reaction occurs[211], it is surprising that the dinuclear Cu(I) complex **216**, containing one bidentate and one monodentate ligand attached to each Cu(I), is able to bind molecular oxygen, this being followed by hydroxylation of the arene moiety. The results presented here show that the aromatic hydroxylation with dinuclear Cu(I) complexes and dioxygen is not specific to a tridentate ligand system and does not depend as critically on the types of donor groups as previously suggested[211].

However, the major part of the reaction pattern by which the product is formed remains unclear. Therefore we decided to investigate the mechanism of this typical reaction by examining several derivatives of **216** as will be presented in the following chapter.

Furthermore we have demonstrated in this investigation, that for the conversion of methyl substituted benzenes to (di)aldehydes, the bromination, hydrolysis procedure is a synthetically very useful method. More examples will follow in chapter 3 and 4. Finally the synthesis of 2,6-substituted phenols via the introduction of the phenolic functionality in 2,6-disubstituted aryl compounds, using copper dioxygen chemistry can be a synthetically useful method for otherwise not easily prepared phenols. An example will follow in chapter 4.

## 2.9 *Experimental part*

**General remarks**

All experiments were performed under an inert ($N_2$) atmosphere when necessary. Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-2 microscope. Infrared spectra were recorded on an Unicam SP-200 Infrared Spectrophotometer. $^1$H NMR spectra were recorded on a Hitachi Perkin Elmer R-24B spectrometer (at 60 MHz), a Nicolet NT-200 spectrometer (at 200 MHz) or on a Varian VXR-300 spectrometer (at 300 MHz). Chemical shifts are for 60 MHz spectra denoted in $\delta$ units (ppm), relative to tetramethylsilane (TMS) as an internal standard at $\delta$ = 0 ppm. For 200 and 300 MHz spectra the $^1$H NMR chemical shifts are determined relative to the solvent and converted to the TMS scale using $\delta(CDCl_3)$ = 7.26 ppm. $^{13}$C NMR spectra were recorded on a Nicolet NT-200 (at 50.32 MHz), or a Varian VXR-300 (at 75.43 MHz) spectrometer. Chemical shifts are determined relative to the solvent and converted to the TMS scale using $\delta(CDCl_3)$ = 76.91 ppm. $^{13}$C-NMR spectra were recorded proton-noise decoupled and proton coupled, the proton coupled spectra were recorded in the gyrogate mode. The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Mass Spectra (MS) and HRMS spectra were recorded on an AEI-MS-902 mass spectrometer (direct inlet temperature ±110°C, acc. voltage 8 kV, voltage 70 eV) and GCMS spectra were recorded on a RIBERMAG R 10-10C mass spectrometer by Mr. A. Kiewiet. X-ray analysis were performed by Mr. F. van Bolhuis and Drs. A. Meetsma from the Crystal Structure Center R.U. Groningen. and by Dr. A.L. Spek from the department of Crystal and Structure Chemistry of the University of Utrecht. Elemental analyses were performed in the microanalytical department of this laboratory by J. Ebels, H. Draaijer, J.V. Hommes, J.E. Vos and A.F. Hamminga. Oxygen sensitive compounds were made and handled using Schlenk equipment and a vacuum line. Nitrogen was deoxygenated by passing it through a copper column. All reagents and solvents were purified, dried and stored under $N_2$ where necessary using standard procedures. The solvents were distilled before use and were stored on molecular sieves (3 or 4 Å). $\alpha,\alpha'$-Dibromo-*m*-xylene, 2-vinylpyridine and $Cu(II)(ClO_4)_2 \cdot 6H_2O$ were purchased from Janssen.

**Isophthalic aldehyde (211)**

This compound was prepared following a literature procedure[30]. A mixture of 15 g (56 mmol) of $\alpha,\alpha'$-dibromo-*m*-xylene (**210**) and 32 g (230 mmol) hexamethylenetetramine was heated at reflux in 150 ml of 50% acetic acid for 2 h.. After this period 75 ml of concentrated hydrochloric acid were added and refluxing was continued for 15 minutes. After cooling, the

solution was neutralized using $Na_2CO_3$ until the evolution of gas ceased. The white precipitate was collected by filtration and dried in vacuo over $P_2O_5$. This resulted in 5.4 g (72%) of white material which was crystallized from $CCl_4$ giving 4.1 g (55%) pure **211** as white needles, m.p. 86.6-87.3°C (lit. 88-90°C); $^1$H NMR ($CDCl_3$): $\delta$ 7.50-7.83 (t, $J$ = 8 Hz, 1H), 8.10 (d, $J$ = 8 Hz, 2H), 8.33 (s, 1H), 10.20 (s, 2H).

**2-(2-pyridyl)ethylamine (213)**

This compound was prepared following a literature procedure[32]. Starting with 26.8 g (0.25 mol) 2-vinylpyridine (**212**) pure **213** was obtained after distillation at 110°C (16 mm Hg) (lit. 90-93°C/9 mm Hg) as a colourless oil: Yield 12.2 g (40%) 2-(2-pyridyl)ethylamine. $^1$H NMR ($CDCl_3$): $\delta$ 1.33 (s, 2H), 3.00 (m, 4H), 6.93-7.20 (m, 2H), 7.33-7.73 (m, 1H), 8.50 (d, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 40.55, 40.69, 119.68, 121.85, 134.72, 147.82, 158.78 ppm.

**1,3-bis[N-(2-(2-pyridyl)ethyl)formimidoyl]benzene (1,3-BPB) (214)**

A mixture of 1.34 g (10 mmol) isophthalic aldehyde (**211**) and 2.44 g (20 mmol) 2-(2-pyridyl)ethylamine (**213**) in 50 ml $CH_2Cl_2$ was stirred for 1 h.. Next, 2 g $Na_2SO_4$ was added and stirring continued for 0.5 h.. Filtration and evaporation of the solvent in vacuo gave 3.10 g (91%) **214** as a colourless oil which was not further purified. Compound **214** was very sensitive to hydrolysis when attempts were made to purify it by chromatography. This material was sufficiently pure according to $^1$H NMR. $^1$H NMR ($CDCl_3$): $\delta$ 3.13 (t, $J$ = 6 Hz, 4H), 3.95 (t, $J$ = 6 Hz, 4H), 7.03 (t, 2H), 7.11 (d, $J$ = 8 Hz, 2H), 7.34 (t, $J$ = 8 Hz, 1H), 7.49 (t, $J$ = 8 Hz, 2H), 7.68 (d, $J$ = 8 Hz, 2H), 7.88 (s, 1H), 8.16 (s, 2H), 8.48 (d, $J$ = 5 Hz, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 38.59, 59.97, 120.25, 122.58, 126.93, 127.77, 128.85, 135.11, 135.59, 148.28, 158.74, 159.81 ppm. HRMS calculated for $C_{22}H_{22}N_4$: 342.184, found: 342.183.

**Tetrakis(acetonitrile)copper(I)tetrafluoroborate (215)**

This complex was prepared according to a literature procedure[33]. Starting from 4.1 g $Cu_2O$ and 23 ml $HBF_4$ (35%), 15.4 g (80%) of **215** was obtained as a white crystalline material after drying in vacuo. The copper(I) complex was stored under a nitrogen atmosphere.

**(1,3-bis[N-(2-(2-pyridyl)ethyl)formimidoyl]benzene)bis(acetonitrile)biscopper(I)tetrafluoroborate (1,3-BPB)$Cu_2(BF_4)_2 \cdot 2CH_3CN \cdot CH_2Cl_2$ (216)**

The preparation of this compound was performed in double Schlenk equipment under a $N_2$ atmosphere. All solvents were made oxygen free by several degassing/saturations with $N_2$ cycles before use. To a suspension of 628 mg (2 mmol) $Cu(CH_3CN)_4BF_4$ (**215**) in 10 ml THF, a solution of 342 mg (1 mmol) of **214** in 10 ml THF was added. After stirring at

room temperature for 16 h. a yellow-orange precipitate had been formed. This precipitate was washed twice with 10 ml THF and dried in vacuo. Attempts to crystallize this precipitate from $CH_2Cl_2/CH_3OH$ (10 : 1) gave small yellow needles unsuitable for X-ray analysis. Total yield of **216** 410 mg (57%). The complex had to be stored under a nitrogen atmosphere. Analysis calculated for $C_{26}H_{28}B_2Cu_2F_8N_6 \cdot CH_2Cl_2$: C: 40.02, H: 3.71, Cl: 8.77, Cu: 15.69, F: 18.77, N: 10.38, found: C: 40.03, H: 3.73, Cl: 8.52, Cu: 15.55, F: 18.66, N: 10.23. When these yellow needles were allowed to stand for a long time in solution, larger yellow needles could be obtained which were suitable for X-ray analysis.

**Crystal structure determination of 216**

The single crystal X-ray determination was performed at room temperature with MoK$\alpha$ radiation ($\lambda$ = 0.71073 Å) on a CAD4F diffractometer equipped with a graphite monochromator and the structure was solved by direct methods (CAD4 SDP-programs, Enraf-Nonius Dreux & Associates). A crystal of dimensions 0.30 x 0.35 x 0.40 nm crystallized in the triclinic space group $P\bar{1}$ with a = 10.003(4), b = 10.979(2), c = 29.763(5) Å, $\alpha$ = 88.83(1), $\beta$ = 81.38(2) and $\gamma$ = 89.91(2)°. Z = 4, $D_c$ = 1.663 gcm$^{-3}$, U = 3220.9 Å$^3$. 3200 unique reflections with I > 3.0 $\sigma$(I) were used in full-matrix least-squares refinement, including H atoms with isotropic thermal parameters, to R = 0.076, $R_w$ = 0.078 (non hydrogen atoms were refined anisotropically). Selected bond distances and angles are given in table 2.1.

**$\mu$-Hydroxo-$\mu$-[2,6-bis[N-(2-(2-pyridyl)ethyl)formimidoyl]phenolato]biscopper(II)tetrafluoroborate $Cu_2$(2,6-BPB-1-O)(OH)$(BF_4)_2$ (221)**

A solution of 200 mg (0.25 mmol) **216** in 40 ml of a mixture of $CH_2Cl_2/CH_3OH$ (10 : 1) was stirred in a reaction vessel open to the atmosphere. Direct after admission of air to the solution of complex **216** a colour change from yellow to dark green was observed. After 3 h. the dark green solution was evaporated to dryness and the residue was crystallized from a $C_2H_5OH/H_2O$ mixture to give dark green, diamond shaped crystals of pure **221**, yield: 110 mg (65%), which were suitable for X-ray analysis. Analysis calculated for $C_{22}H_{22}B_2Cu_2F_8N_4O_2$: C: 39.14, H: 3.28, Cu: 18.82, F: 22.51, N: 8.30, found: C: 39.12, H: 3.41, Cu: 18.65, F: 22.00, N: 8.56. IR(KBr): 1575, 1640, 3500 cm$^{-1}$.

When this reaction was carried out in a closed system connected to a gas burette under an oxygen atmosphere using $CH_3OH$ as the solvent, a stoichiometric reaction between dioxygen and **216** was found. Thus in a particular example 400 mg (0.5 mmol) of **216** was reacted in a thermostatic bath at 18°C with dioxygen. After three minutes 9.5 ml oxygen was consumed, whereas when the reaction time was prolonged to 1 h. a total volume of 10.5(±1) ml (90% based on **216**) was consumed.

The phenolic ligand was liberated from complex **221** by an ammonia/$CH_2Cl_2$ extraction procedure. The complex (100 mg) was shaken for 2 minutes with a mixture of 30 ml $CH_2Cl_2$ and 30 ml concentrated ammonia. The $CH_2Cl_2$ layer was separated and washed two times with 10 ml ammonia. The ammonia layers were combined and extracted with 10 ml $CH_2Cl_2$. The combined $CH_2Cl_2$ layers were dried over $Na_2SO_4$ and filtrated. Evaporation of the solvent gave 40 mg (75%) of **222** as a yellow oil - pure material by $^1H$ NMR - which was not further purified. $^1H$ NMR ($CDCl_3$): $\delta$ 3.15 (t, $J$ = 7.4 Hz, 4H), 4.00 (t, $J$ = 7.4 Hz, 4H), 6.85 (t, $J$ = 7.7 Hz, 1H), 7.04-7.20 (m, 4H), 7.49-7.62 (m, 4H), 8.43-8.56 (m, 4H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 38.49, 58.88, 117.14, 120.47, 122.62, 131.00, 135.40, 148.29, 158.34, 160.29, 160.58 ppm. HRMS calculated for $C_{22}H_{22}N_4O$: 358.179, found: 358.177.

**2,6-dimethylacetoxybenzene (225)**

To a stirring solution of 12.2 g (0.1 mol) 2,6-dimethylphenol (**223**) and 11.0 g (0.11 mol) triethylamine in 100 ml $CH_2Cl_2$ was added 8.0 g (0.102 mol) acetylchloride at such a rate that the solution was gently refluxing. Stirring was continued for 1 h. at room temperature and subsequently 100 ml of $H_2O$ was added. The $CH_2Cl_2$ layer was separated and washed successively with 1 N HCl (2 x 30 ml), 1 N NaOH (2 x 30 ml) and 1 N HCl (30 ml). After drying over $MgSO_4$ and filtration, the solvent was evaporated and the oily residue was distilled at 100°C (16 mm Hg), using a Kugelrohr distillation apparatus to give 13.5 g (83%) of pure **225** as a colourless oil. $^1H$ NMR ($CDCl_3$): $\delta$ 2.16 (s, 6H), 2.35 (s, 3H), 7.06 (s, 3H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 16.19, 20.36, 125.70, 128.40, 129.92, 148.04, 168.60 ppm. HRMS calculated for $C_{10}H_{12}O_2$: 164.084, found: 164.084.

**2,6-($\alpha,\alpha,\alpha',\alpha'$-tetrabromo)dimethylacetoxybenzene (226)**

In a three necked flask, fitted with a reflux condensor connected with a watertrap, a solution of 10 g (60 mmol) of **225** in 100 ml $CCl_4$ was placed together with some glasspearls. Under continuous irradiation with a Philips IR133372E/44*E9 photolamp, 12.3 ml (240 mmol) of bromine was slowly added over a 2 h. period while the solution was gently refluxing. After the addition was completed, the resulting mixture was heated and irradiated for an additional period of 12 h.. By that time the bromine had completely disappeared. The solvent was removed by distillation and the solid residue purified by crystallization from hexane/$CHCl_3$, affording **226** as white crystalline material. Yield: 20.0 g (70%). m.p. 142.6-143.4°C; $^1H$ NMR ($CDCl_3$): $\delta$ 2.43 (s, 3H), 6.60 (s, 2H), 7.20-7.56 (m, 1H), 7.90 (d, $J$ = 7.2 Hz, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.77, 32.87, 127.60, 131.74, 134.19, 139.70, 167.66. Analysis calculated for $C_{10}H_8Br_4O_2$: C: 25.03, H: 1.68, Br: 66.62, found C: 25.01, H: 1.63, Br: 66.82. HRMS calculated for $C_{10}H_8Br_4O_2$: 475.726, found: 475.727.

**1-hydroxybenzene-2,6-dicarboxaldehyde (228)**

A slurry of 6.0 g (12.5 mmol) **226** in concentrated sulphuric acid (50 ml) was stirred for 16 h. at room temperature. The resulting solution was poured onto 100 g crushed ice and the aqueous mixture was extracted with ether (3 x 100 ml). (Caution, gloves should be used in order to protect the skin). The ether layers were combined, dried over $MgSO_4$ and evaporated to dryness. The white solid residue was crystallized from $H_2O$ giving 1.1 g (58%) of **228** as white crystals. m.p. 120.3-121.5°C; $^1$H NMR ($CDCl_3$): $\delta$ 7.02-7.33 (m, 1H), 8.03 (d, $J$ = 7.6 Hz, 2H), 10.56 (s, 2H), 12.00 (s, 1H); $^{13}$C NMR ($CDCl_3$ at 50°C): $\delta$ 119.79, 123.18, 137.43, 163.53, 191.79 ppm. HRMS calculated for $C_8H_6O_3$: 150.032, found: 150.031.

When this hydrolysis was done at 60°C, only the 4-bromo-substituted analog **227** could be isolated in 65% yield after crystallization. m.p. 134.8-135.6°C; $^1$H NMR ($CDCl_3$): $\delta$ 8.03 (s, 2H), 10.30 (s, 2H), 11.62 (s, 1H). Analysis calculated for $C_8H_5BrO_3$: C: 41.92, H: 2.18, found: C: 41.91, H: 2.25.

**2,6-bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-1-hydroxybenzene (2,6-BPB-1-OH) (222)**

This compound was prepared following the same procedure as described for **214**. Starting with 150 mg (1 mmol) of **228** and 244 mg (2 mmol) of 2-(2-pyridyl)ethylamine (**213**), 320 mg (88%) of **222** was obtained as a yellow oil. This material was sufficiently pure ($^1$H NMR) and was identical in all respects with the compound obtained earlier from the oxidation and subsequent ammonolysis of **216**.

**$\mu$-Hydroxo-$\mu$-[2,6-bis[N-(2-(2-pyridyl)ethyl)formimidoyl]phenolato]biscopper(II)perchloraat $Cu_2$(2,6-BPB-1-O)(OH)($ClO_4$)$_2$ (229)**

A mixture of 358 mg (1.0 mmol) of **222**, 800 mg (2.2 mmol) $Cu(ClO_4)_2 \cdot 6H_2O$ and 80 mg (2.0 mmol) NaOH in 50 ml $CH_3OH$ was refluxed for 3 h. giving a dark green coloured solution. Evaporation of the solvent gave a dark green residue which was crystallized from $CH_3OH/H_2O$ to give 410 mg (58%) of **229** as dark green crystals. Analysis calculated for $C_{22}H_{22}Cl_2Cu_2N_4O_{10}$: C: 37.71, H: 3.14, Cl: 10.14, Cu: 18.14, N: 8.00, found: C: 37.79, H: 3.19, Cl: 10.73, Cu: 17.80, N: 8.00. IR (KBr): 1090, 1560, 1630 and 3500 cm$^{-1}$.

**Crystal structure determination of 221**

The single crystal X-ray determination was performed at low temperature with MoK$\alpha$ radiation ($\lambda$ = 0.71073 Å) on an Enraf-Nonius CAD-4F diffractometer equipped with a graphite monochromator and interphased to a PDP11/23 using the w-2$\Theta$ scan technique. A crystal of dimension 0.30 x 0.25 x 0.04 mm was obtained by crystallization from an

$C_2H_5OH/H_2O$ mixture, and crystallized in the triclinic space group $P\bar{1}$ with a = 9.323(4), b = 10.449(2), c = 14.179(4) Å, $\alpha$ = 102.30(4), $\beta$ = 102.43(2), $\gamma$ = 101.84(2)° and V = 1271.5(6) $Å^3$. For Z = 2 the calculated density is 1.763 $gcm^{-3}$. For 1.53° < $\Theta$ < 27.0° 5873 reflections were obtained, 5524 reflections with I ≥ 2.5 $\sigma$(I) were only used in the refinements. The structure was solved by Patterson methods and subsequent partial structure expansion using the SHELXS86 program[45]. Some disorder was found: in a difference Fourier map without C(21) and C(22) four peaks of nearly equal electron density were located on positions with chemically reasonable geometry for C - C bonds, Carbon atoms were introduced on this positions with a site occupancy factor of 0.5 and subsequently refined satisfactory. Hydrogen atoms located on a difference Fourier map were included in the final refinements with isotropic temperature factors. All calculations were carried out on a CDC-Cyber 170/760 computer with the program packages XTAL[46], EUCLID[47] and a modified version of the program PLUTO. The structure was refined to R = 0.044 with the non-hydrogen atoms anisotropically refined. Selected bond distances and angles are given in Table 2.2.

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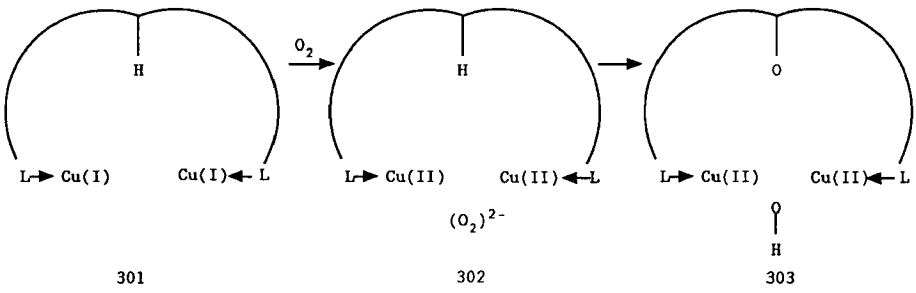
# CHAPTER 3

## BISCOPPER(I)-PROMOTED HYDROXYLATIONS
## A MECHANISTIC INVESTIGATION

### 3.1 *Introduction*

In the previous chapter a remarkable oxygen insertion reaction into an arene C - H bond of a dinuclear Cu(I) complex was found. This could serve as a monooxygenase model system. In this chapter several modifications in the ligand system are made in order to obtain more insight into the mechanism of this insertion reaction.

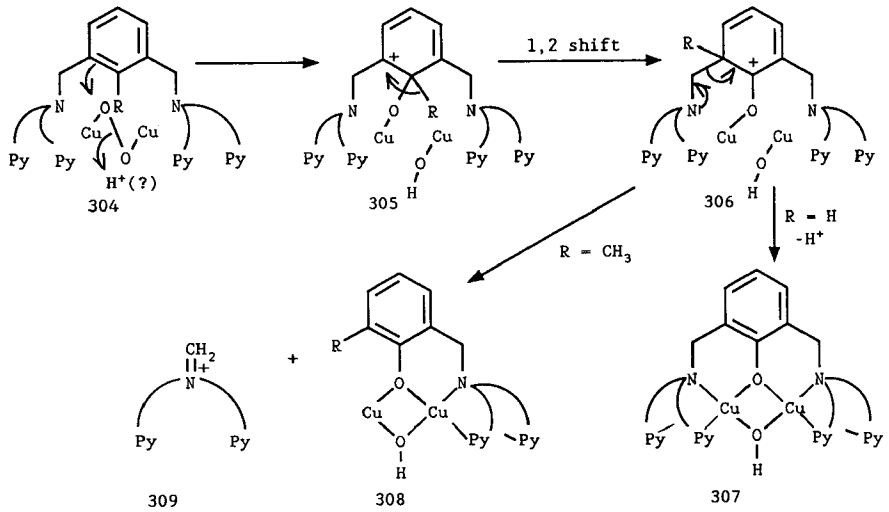
Although it is well accepted that in the first step of the reaction of dinuclear Cu(I) complexes **301** with molecular oxygen a peroxo dicopper(II) species **302** will be formed[1] (scheme 3.1), little is known about the degradation of this peroxo intermediate to form the oxygenated products such as **303**. With regard to the monooxygenases, such as tyrosinase, Daily[2] and Solomon[3] suggested that hydroxylation in these enzymes proceeds via electrophilic attack on aromatic substrates (see also section 2.1) followed by O - O bond cleavage.




*Scheme 3.1*

Karlin and co-workers have observed the first example of an arene hydroxylation with $O_2$ in a related dinuclear Cu(I) complex[4] (see also section

2.3). The overall reaction is shown in scheme 3.2. In a mechanistic interpretation they propose that an intermediate electrophilic dioxygen complex attacks the arene ligand. When **306** (R = H) loses a $H^+$, the phenoxy-hydroxy bridged dinuclear Cu(II) complex **307** is formed. This conclusion is further based on experiments where the hydrogen atom in the 1-position of the xylyl bridge is replaced by a methyl substituent (**304,** R = $CH_3$). Upon reaction with dioxygen a peroxo dicopper(II) complex **304** is initially formed. This complex degrades to form copper(II) complex **308** and the iminium ion **309**. To account for these degradation products, first a 1,2-migration of the methyl substituent (**305** → **306**, R = $CH_3$) must have taken place. In a subsequent step the loss of the iminium ion **309**, in a retro Mannich reaction, is assisted by the electron lone pair on the amine nitrogen atom[1c]. These findings are typical for an electrophilic pathway and are in accordance with the suggestions made by Daily[2] and Solomon[3] that oxygenations via copper monooxygenases, such as tyrosinase, proceed by an electrophilic attack of a bis-copper-peroxide on the aromatic substrate.

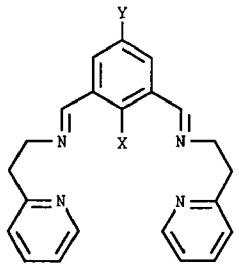



*Scheme 3.2*

Other findings however, e.g. ready protonation of the peroxide in different types of $(Cu_2O_2)^{2+}$ complexes, indicate the nucleophilic character of this species[6].

As was described in chapter 2 the major differences in our monooxygenase model and that of Karlin are the bidentate vs. tridentate nature of the ligand available for each Cu(I) center and the presence of an aryl bisimine instead of a bis(aminomethylene)aryl moiety.

Our approach to obtain more insight into the reaction mechanism was to modify the substitution pattern (**X**) of the aromatic nucleus of ligand **310** at the carbon center C-1, which is most vulnerable to oxygenation (fig. 3.1).




310

*Figure 3.1*

It is to be expected that the observed oxidation chemistry can give us more information about the nature of the oxygenating species and the electronic (and steric) requirements or limits for oxygen insertion.

Another approach could be the introduction of different substituents (**Y**) into the para position of the reacting carbon center. A kinetic investigation could then give clues about the nature of the intermediates formed during this reaction. Attempts along this second approach were made but the oxygenation reaction appeared to proceed too fast to measure accurately the electronic effects of *p*-methyl, *p*-nitro and *p*-methoxy substituted analogs of our basic

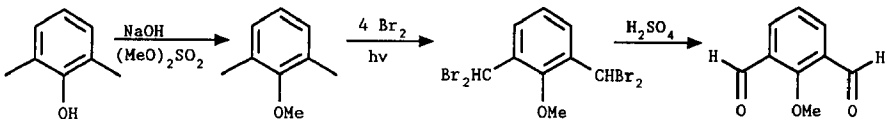
system[7]. Thus most of our attention was paid to the preparation of a number of C-1 substituted analogs of **310**.

The findings described in this chapter are not consonant with a hydroxylation via an electrophilic peroxo dicopper(II) species as is suggested by Karlin[5,8], but point to a nucleophilic character of this peroxo dicopper(II) species.

### 3.2 *Synthesis of the C-1-modified ligands*

In this study methyl, methoxy and halogen substituents (X in **310**) were introduced in the C-1 position to examine the effects of C - C and C - hetero bonds and electron donating as well as withdrawing groups in the hydroxylation reactions.

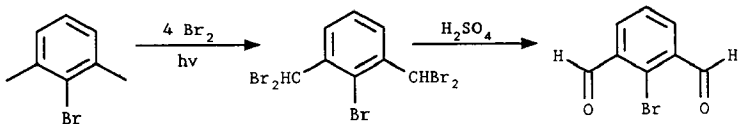
In the first derivative a methoxy substituent was introduced at C-1 according to scheme 3.3. Starting with 2,6-dimethylphenol (**311**), the phenol group was protected via ether formation with NaOH and dimethyl sulfate to give **312** in 90% yield after distillation. Next the tetrabromination, followed by hydrolysis, as described earlier in section 2.6, was used to prepare 1-methoxybenzene-2,6-dicarboxaldehyde (**314**) in 45% overall yield from **312**.




311 312 313 314

*Scheme 3.3*

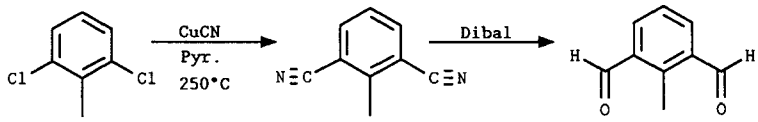
The second derivative, 1-bromobenzene-2,6-dicarboxaldehyde (**317**), was prepared in two steps starting from 1-bromo-2,6-dimethylbenzene (**315**). Using the same bromination, hydrolysis sequence as described for **314**, **317** could be obtained in 60% overall yield (scheme 3.4).




315 316 317

*Scheme 3.4*

The third derivative, 1-methylbenzene-2,6-dicarboxaldehyde (**320**) was prepared in two steps starting from 2,6-dichlorotoluene (**318**) (scheme 3.5). For **320** the bromination, hydrolysis sequence could not be used for obvious reasons. In the first step a Rosenmund - von Braun reaction using CuCN in pyridine was performed on **318**, giving the crystalline 2,6-dicyanotoluene (**319**) in 32% yield. The dinitrile **319** was then reduced by the sterically hindered and mild reducing agent diisobutyl aluminiumhydride, to give, after hydrolysis, 2-methylbenzene-1,3-dicarboxaldehyde (**320**) as white crystalline material in 50% yield.

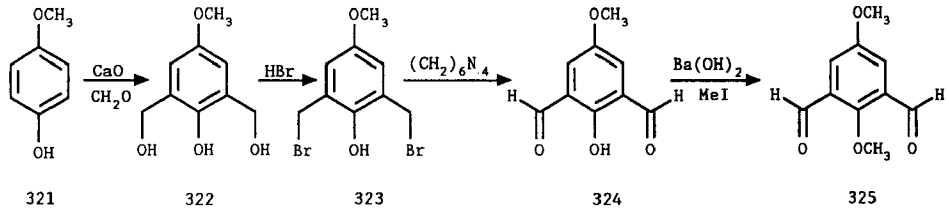



318 319 320

*Scheme 3.5*

The last derivative in this series of C-1 modified dialdehydes was 1,4-dimethoxybenzene-2,6-dicarboxaldehyde (**325**). This compound was prepared according to scheme 3.6. Although for the dialdehyde **325** the bromination, hydrolysis sequence might be used starting from 2,6-dimethyl-1,4-hydroquinone, a shorter route was used. Starting with hydroquinone-monomethylether (**321**) two hydroxymethyl groups were introduced by reaction of **321** with CaO and formaldehyde in 75% yield according to a literature procedure[10]. Direct oxidation of the hydroxymethyl substituents in **322** to the corresponding aldehydes failed; therefore the hydroxymethyl groups were converted to

bromomethyl groups by reaction of **322** with HBr. This reaction gave $\alpha^2,\alpha^6$-dibromo-2,6-dimethyl-4-methoxyphenol (**323**) in 80% yield.

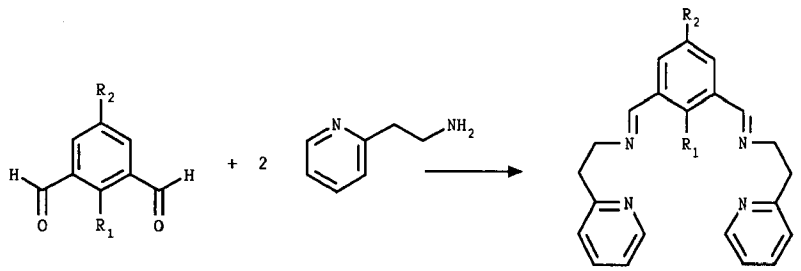



321 322 323 324 325

*Scheme 3.6*

Attempts to protect the phenolic unit via its methyl ether failed because of the lability of the bromomethyl groups. A Sommelet reaction[11] performed on **323** gave the corresponding dialdehyde **324** in 30% yield as a yellow crystalline material. Methylation of the phenolic unit could not be performed using standard conditions (NaOH, $(CH_3O)_2SO_2$) because of the instability of aldehydes towards aqueous base. But a reaction using $Ba(OH)_2 \cdot H_2O$ and $CH_3I$ in DMF gave 55% yield of the desired product **325**.

The four new dialdehydes **314**, **317**, **320** and **325** described here could easily be purified by crystallization from various solvents. This resulted in crystalline materials which were pure as judged by elemental analysis, sharp melting points and distinct sharp $^1H$ NMR spectra (a singlet for all compounds in the 10-11 ppm region, accounting for the aldehyde protons was observed). They were easily converted into the corresponding diimine ligands by condensation with two equivalents of 2-(2-pyridyl)ethylamine (**213**) in 90-95% yields (scheme 3.7). All the diimines were sufficiently pure for further use as judged from the $^{13}C$ and $^1H$ NMR spectra. Characteristic is the upfield shift of the aldehyde protons of about 2 ppm when converted into the imine form.



314: $R_1$ = OMe, $R_2$ = H
317: $R_1$ = Br, $R_2$ = H
320: $R_1$ = Me, $R_2$ = H
325: $R_1$ = OMe, $R_2$ = OMe

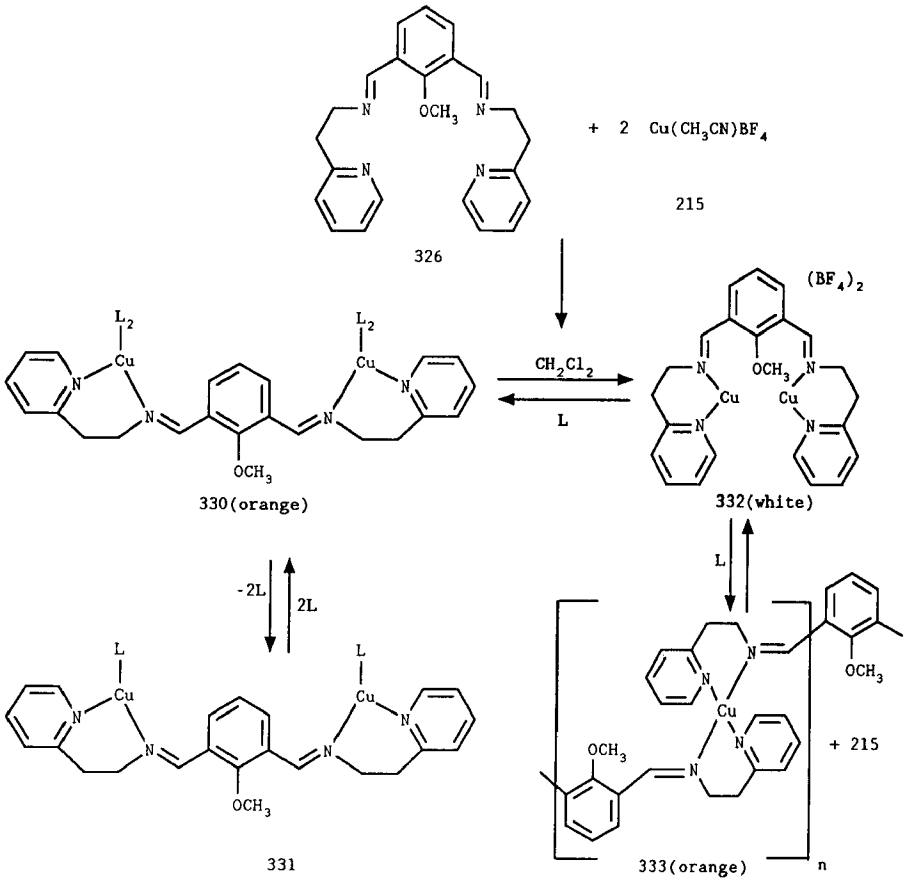
326: $R_1$ = OMe, $R_2$ = H (2,6-BPB-1-OMe)
327: $R_1$ = Br, $R_2$ = H (2,6-BPB-1-Br)
328: $R_1$ = Me, $R_2$ = H (1,3-BPB-2-Me)
329: $R_1$ = OMe, $R_2$ = OMe (2,6-BPB-1,4-OMe)

*Scheme 3.7*

## 3.3 *Complexations of the C-1 substituted ligands 326, 327, 328 and 329 with Cu(I).*

### *3.3.1 Complexation of 2,6-bis[N-(2-(2-pyridyl)ethyl)formimidoyl] -1-methoxybenzene (326) with $Cu(CH_3CN)_4BF_4$*

In this section the "all-round" coordination ability of **326** with Cu(I) will be described, leading to chameleon-like complexation behavior. When the ligand **326** was allowed to react with two equivalents of $Cu(CH_3CH)_4BF_4$ in THF, under a nitrogen atmosphere, an orange precipitate was formed in 90% yield (scheme 3.8). Combustion analysis of this precipitate gave a formula of $C_{31}H_{36}B_2Cu_2F_8N_8O$ and a Cu - N ratio of 1 : 4. When, however, this precipitate was washed several times with THF a lower Cu : N ratio was found, indicating that some nitrogen containing ligands (presumably $CH_3CN$) are weakly bound to the dicopper(I) complex. In the $^1H$ NMR a singlet for 12 protons at 2.08 ppm was found. This originates from four identical acetonitrile ligands. Based on these findings we presume that the complex contains two four coordinated Cu(I) centers. Two of the coordination sites around each Cu(I) ion are occupied by $CH_3CN$ whereas the other two are occupied by a pyridylethylimine-bidentate unit giving complex **330**.



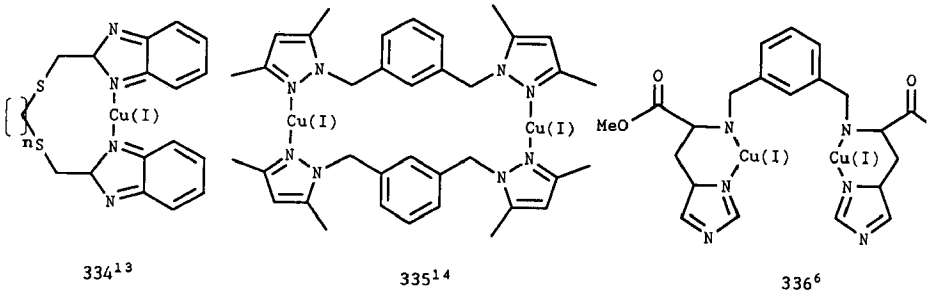

*Scheme 3.8: Chameleon-like complexation behavior (L = $CH_3CN$)*

Attempts to get crystals of **330** suitable for an X-ray structure determination failed. Complex **330** is stable to dioxygen in its solid state but readily reacts with dioxygen when it goes into solution. Presumably, in solution **330** is in equilibrium with the three coordinated complex **331**, because of the weakly bound fourth acetonitrile ligand. The easy formation of three coordinated complex **331** by loss of $CH_3CN$ is supported by the isolation of the three coordinated desmethoxy analog **216**, which was described in section 2.4.

When **330** is heated under reflux in $CH_2Cl_2$ for 10 minutes a colour change from orange to colourless is observed and a white precipitate appears.

This white precipitate was washed several times by $CH_3OH$ and isolated in 58% yield. Elemental analysis of this complex showed a Cu : N ratio of 1 : 2 and a bruto formula of $C_{23}H_{24}B_2Cu_2F_8N_4 \cdot 0.5CH_2Cl_2$. $^1H$ NMR in $d_6$-DMSO showed a symmetric coordination of the ligand with a downfield shift of 0.1-0.2 ppm for all protons with the largest downfield shift for the methoxy protons (0.23 ppm) compared to the free ligand. The white complex is poorly soluble in solvents like $CH_2Cl_2$, THF, $CH_3OH$, DMF and very stable in its solid state towards dioxygen. Although two coordination of each copper center is most likely[12] it cannot be excluded that a three coordinated structure is present due to methoxy bridging or the occurrence of Cu(I) - Cu(I) bonding in **332**. The copper ions in **332** might also expand their coordination number through intermolecular interactions and in this way form polymeric, poorly soluble, structures.

Two coordination around Cu(I) is known to exist in a number of compounds. Reedijk and co-workers[13] reported a linear two coordinated Cu(I) ion in the cation Cu(I)BBDHP$^+$ (**334**) (figure 3.2). In section 2.5 an example was shown of a dinuclear two coordinated Cu(I) complex[14] **335**. A histamine-derived dinuclear Cu(I) complex **336** with proposed two coordination has been reported although no X-ray analysis could be obtained[6].




334[13] 335[14] 336[6]

*Figure 3.2: Some examples of two-coordinated Cu(I) complexes*

When complex **332** was dissolved in $CH_2Cl_2$ or $CHCl_3$ and four equivalents of $CH_3CN$ were added the orange colour indicating the presence of **330** reappeared. After being stirred for 2 h. at room temperature THF was added upon which an orange precipitate formed. After filtration and drying in vacuo dinuclear Cu(I) complex **330** (80-90%) was obtained, in all respects identical with **330** prepared from **326** and $Cu(CH_3CN)_4BF_4$. The conversion of **330** to **332** and vice versa could be repeated several times with small (10-20%) loss of material. Karlin and co-workers have reported a related case where reversible $CH_3CN$ binding takes place in $CH_2Cl_2$/ether mixtures[15].

However, when an excess of $CH_3CN$ is added to a suspension of **332** in $CHCl_3$ and the resulting solution was allowed to stand for a period of 50 h., a mixture of a white crystalline and an orange crystalline material could be obtained in about a 1 : 1 ratio. These crystals could be separated manually. The white material appeared to be $Cu(CH_3CN)_4BF_4$ (on basis of $^1H$ NMR (one singlet) and IR spectra). The orange crystals were suitable for an X-ray analysis. This revealed (vide infra) that a helical coordination polymer had been formed with Cu(I) ions as linkers between two pyridylethylimine units of different molecules (scheme 3.8). In this complex each Cu(I) ion coordinates to two ligands giving a tetrahedal geometry. The ligand - copper stoichiometry in **333** is 1 : 1 instead of 1 : 2 in the complexes **330** and **332.** When the mixture of **333** and $Cu(CH_3CN)_4BF_4$ is allowed to react with dioxygen in $CH_2Cl_2/CH_3OH$, the same oxygenation products are found as those obtained from the oxidation of **330.** This indicates a reversible reaction of **333** and $Cu(CH_3CN)_4$ to **330** probably via the intermediate **332.**

The findings described in this section showed a chameleon-like coordination behavior of Cu(I) towards the ligand **326.** It is surprising that **331,** which is the three (nitrogen donors) coordinated dinuclear Cu(I) complex, could not be isolated whereas the desmethoxy analog was readily obtained and characterized by X-ray analysis (section 2.5). Furthermore the various equilibria **330** ⇄ **332, 330** ⇄ **331** and **332** ⇄ **333** make this complexation behavior not

easily predictable. Obviously, these equilibria are very vulnerable to subtle changes in the ligand or in the solvent mixtures.

*3.3.2 X-ray analysis of coordination polymer 333*

Crystallization of **333** from a $CHCl_3/CH_3CN$ mixture afforded bright orange crystals which were suitable for an X-ray analysis. The complex crystallizes in the monoclinic space group $P2_1/n$ with an independent unit structure as depicted in figure 3.3a. Upon coordination of Cu(I) the ligand **326** has formed a linear coordination polymer with two helical strands, one right and one left handed, lying next to each other in the infinite unit cell. The cell parameters are a = 13.826(3), b = 9.938(2), c = 20.555(6) Å, $\alpha$ = 90.0, $\beta$ = 102.58(2), $\gamma$ = 90.0° and Z = 1. Each unit cell contained one molecule of $CHCl_3$. The final refinement (R index) was 0.059. The crystal structure with adopted numbering scheme and a stereoplot are depicted in figure 3.3. Selected bond distances and angles are given in table 3.1. Each Cu(I) atom is surrounded by four N-atoms in a distorted tetragonal geometry. The Cu - N distances are nearly the same (2.03-2.09 Å) and on average slightly longer than the Cu - N distances in the three coordinated complex **216** as described in section 2.5, as was expected on basis of steric repulsions. The Cu - $N_{pyr}$ distances (2.08 Å) are rather long compared to the Cu - $N_{pyr}$ distances generally found for tetracoordinated Cu(I) ions (2.0-2.05 Å)[16], but are quite similar to the Cu - $N_{pyr}$ distances found in the three coordinated complex **216**.

Owing to the difficulty of obtaining single crystals relatively few X-ray structure determinations have been carried out on coordination polymers. In **333** the Cu(I) ion is an integral part of the polymer backbone forming a linear structure. Other polymers with backbone metals are known which form linear, planar or three dimensional structures depending on the identity of the ligand and the coordination abilities of the metal ion[17,18]. A few structures of copper(I) coordination polymers have appeared in the literature. Reedijk and co-workers recently described a reaction of N,N,N',N'-tetrakis(pyrazole -1'-ylmethyl)-1,2-diaminoethane (edtp) with $Cu(CH_3CN)_4BF_4$ which produced a

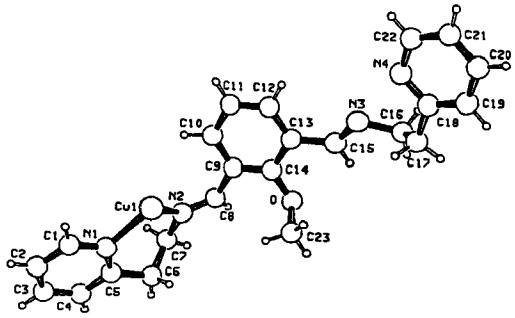



*Figure 3.3.a: Crystal structure of **333**; only one monomer is shown*

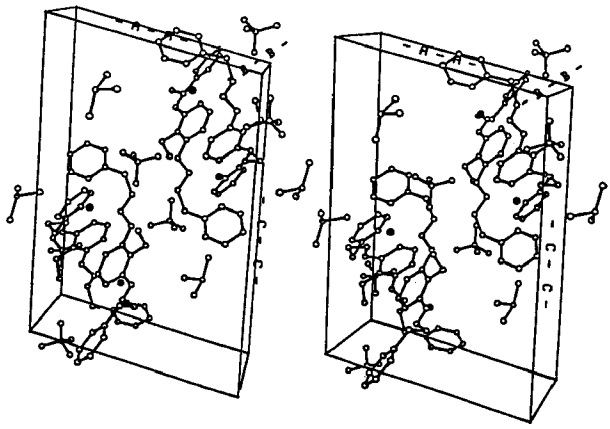


*Figure 3.3.b: Stereo-packing diagram of **333***

*Table 3.1: Selected bond distances (Å) and angles (deg) for 333*

| | | | |
|---|---|---|---|
| Cu(1) - N(1) | 2.097(5) | N(1) - Cu(1) - N(2) | 97.0(2) |
| Cu(1) - N(2) | 2.032(5) | N(1) - Cu(1) - N(3)$^1$ | 107.4(2) |
| Cu(1) - N(3)$^1$ | 2.048(4) | N(1) - Cu(1) - N(4)$^1$ | 109.6(2) |
| Cu(1) - N(4)$^1$ | 2.073(5) | N(2) - Cu(1) - N(3)$^1$ | 131.2(2) |
| Cu(1) - Cu(1)$^1$ | 7.650(4) | N(2) - Cu(1) - N(4)$^1$ | 111.9(2) |
| | | N(3)$^1$- Cu(1) - N(4)$^1$ | 98.9(2) |

white Cu(edtp)$BF_4CH_3CN$ linear polymer. The Cu(I) ions are coordinated by four pyrazole N-atoms in an almost tetrahedral arrangement[19]. Fares and co-workers reported a polymeric cyano-2,2'-biquinoline-Cu(I) complex containing both linear and tetrahedrally coordinated Cu(I) in the chain[20].

In the present coordination polymer **333** two helical strands are present in the unit cell and this unique coordination mode relates to the Cu(I) coordinated double stranded helicates which were reported by Lehn and Rigault[21] in their self assembling poly-bipyridine ligand systems (figure 3.4).

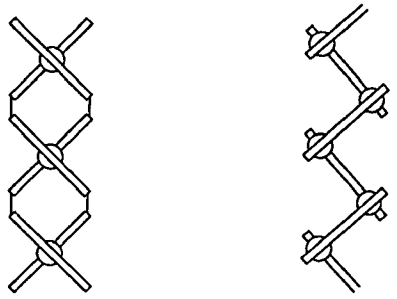


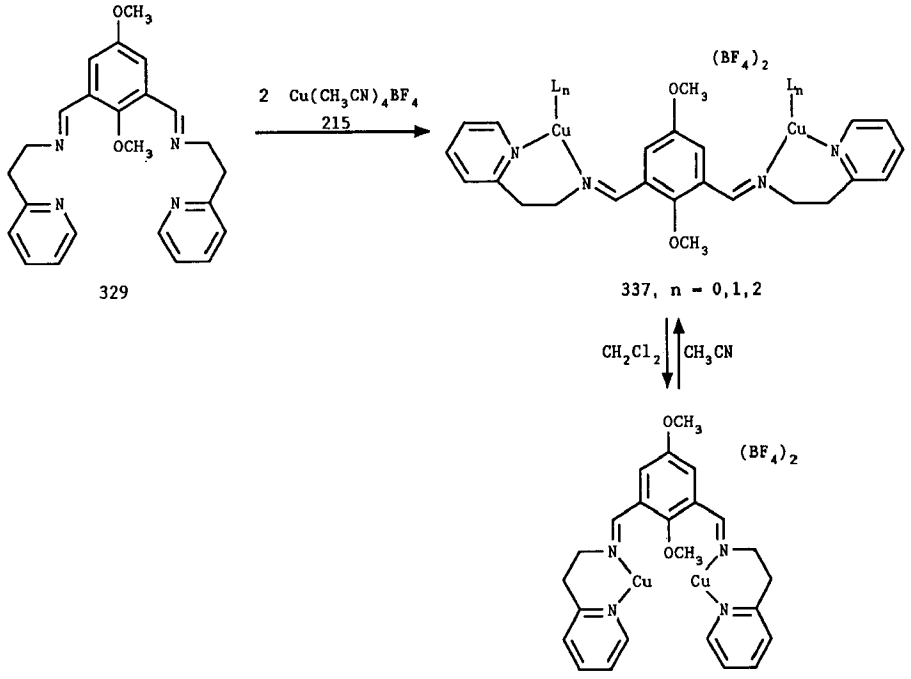

*Figure 3.4: Schematic representation of the helical structures of Lehn and Sauvage[21] (left) and 333 (right)*

In our system the two helixes are single stranded and are of opposite chirality. The methoxy substituent in the ligand points to the outside of the helicate, thereby minimizing steric hindrance. All these coordination polymer complexes are interesting with regard to their expected organic, inorganic, physical and

biochemical properties such as self assembly, supramolecular structures for recognition, material properties etc..

### *3.3.3 Complexation of 2,6-bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-1,4-dimethoxybenzene (329) with $Cu(CH_3CN)_4BF_4$*

When a solution of **329** in THF was allowed to react with a suspension of two equivalents of $Cu(CH_3CN)_4BF_4$ in THF under an inert atmosphere an orange precipitate was formed in 80% yield. Attempted crystallization of this precipitate from $CH_2Cl_2$/ether mixtures failed and gave only a precipitate with a Cu : N ratio of 1 : 3.6. This means that four as well as three (or two) coordinated Cu(I) centers are present. Unfortunately no satisfactory analysis for the tetra acetonitrile coordinated complex **337** was obtained. Pure dinuclear complex **338** (60%), without coordinating acetonitrile ligands, was obtained however, when **337** was boiled in $CH_2Cl_2$ and subsequently washed with $CH_3OH$ (scheme 3.9).




329

337, n = 0,1,2

338

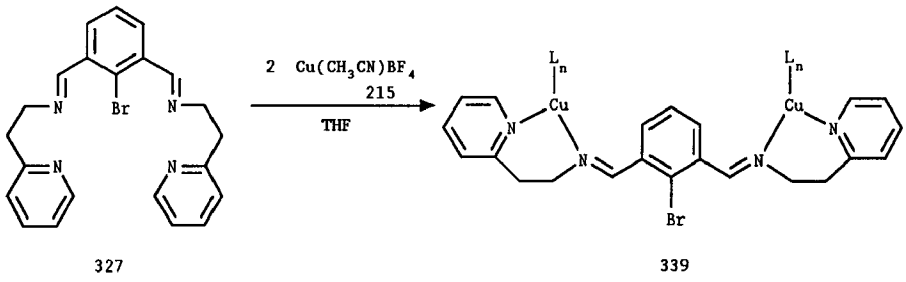
*Scheme 3.9 (L = $CH_3CN$)*

Elemental analysis of **338** gave a formula of $C_{24}H_{26}Cu_2F_8N_4O_2$ indicating either two coordination around each Cu(I) ion or perhaps methoxy bridging (see also section 3.3.1). Addition of excess of $CH_3CN$ to a suspension of **338** in $CH_2Cl_2$ reconverted this complex to **337**, completely in agreement with the reversible $CH_3CN$ binding observed for **332.**

As a consequence of the difficulties we had encountered in the isolation of various Cu(I) complexes such as **330, 332** and **216,** having two, three or four coordination around the Cu(I) ions we decided to take no further efforts in trying to crystallize **337** and **338.**

### *3.3.4 Complexation of 2,6-bis[N-(2-(2-pyridyl)ethyl)formimidoyl] -1-bromobenzene (327) with $Cu(CH_3CN)_4BF_4$*

In the same manner as described for **329**, the ligand **327** was allowed to react with two equivalents of $Cu(CH_3CN)_4BF_4$, to form an orange precipitate in 85% yield. This precipitate was washed several times with THF. After drying in vacuo an orange solid was obtained which contained two Cu(I) ions per molecule of **327** as demonstrated by elemental analysis. The Cu : N ratio was 1 : 2.9. This means that both two and three and probably four coordinated centers are present. Owing to the difficulties we had encountered before in purifying Cu(I) salts this precipitate was not further purified and was used as such (scheme 3.10).

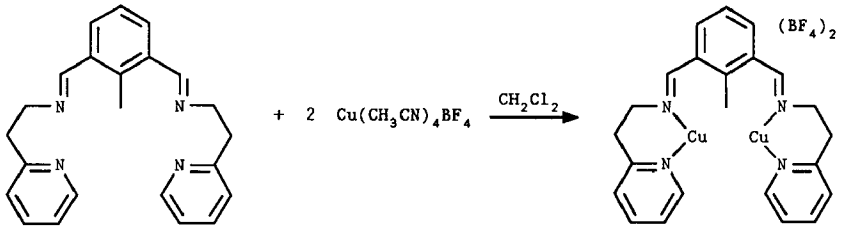



327 339

*Scheme 3.10 (L = $CH_3CN$)*

### *3.3.5 Complexation of 1,3-bis[N-(2-(2-pyridyl)ethyl)formimidoyl] -2-methylbenzene (328) with $Cu(CH_3CN)_4BF_4$*

For the preparation of the final dinuclear Cu(I) complex in the C-1 substituted series, **328** was allowed to react with two equivalents of $Cu(CH_3CN)_4BF_4$ forming an orange precipitate which was boiled for 15 minutes in $CH_2Cl_2$ to give a white precipitate **340** in 65% yield (scheme 3.11). Elemental analysis of this precipitate revealed a formula of $C_{23}H_{24}Cu_2N_4B_2F_8$ indicating that each copper ion is coordinated by two nitrogen atoms.



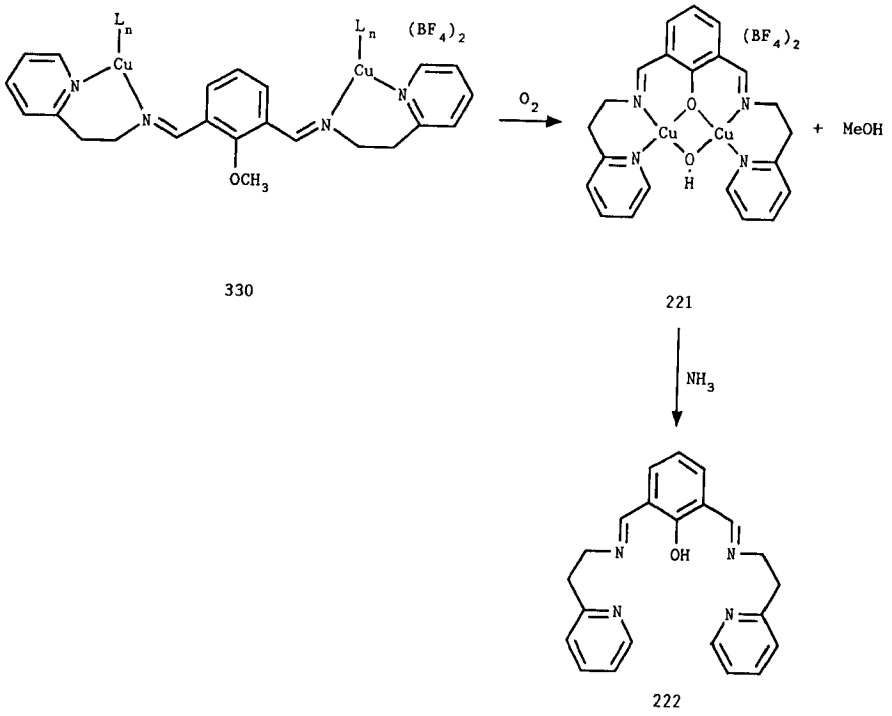

328 215 340

*Scheme 3.11*

The preparations of the C-1 substituted derivatives of our original ligand **214** have been described thus far. These ligands showed a complicated coordination behavior towards $Cu(CH_3CN)_4BF_4$. All the ligands prepared were capable of binding two Cu(I) ions. The coordination of acetonitrile differed for these complexes. This difficulty was not present in the hydroxylation reactions as described in the following section. All hydroxylation reactions were carried out in $CH_2Cl_2/CH_3OH$ mixtures using the acetonitrile coordinated complexes **330**, **337** and **339**, or in $CH_2Cl_2/CH_3OH/CH_3CN$ mixtures using the complexes **332**, **338**, **339** and **340**. In this manner the latter were converted, in situ, to the acetonitrile coordinated complexes. Following both procedures the same oxidation products were obtained.

### 3.4 *Reaction of $Cu_2$(2,6-BPB-1-$OCH_3$)$(BF_4)_2(CH_3CN)_4$ (330) with molecular oxygen*

When 0.5 mmol of complex **330** was dissolved in 10 ml $CH_2Cl_2$ or a $CH_2Cl_2/CH_3OH$ (10 : 1) mixture and subsequently exposed to the air, a rapid change of the colour from orange to dark green was observed. Manometric experiments showed a stoichiometric reaction of one equivalent of **330** with one equivalent of $O_2$. Oxygen uptake was completed in 1 h. at room temperature. The reaction product, a green solid material, was purified by crystallization from $C_2H_5OH/H_2O$ and isolated in 85% yield. Elemental analysis was in accord with a complex with bruto formula $C_{22}H_{22}B_2Cu_2F_8N_4O_2 \cdot H_2O$ and X-ray analysis of this product revealed a structure analogous to the dinuclear Cu(II) complex **221** obtained via the arene hydroxylation described in the previous chapter (scheme 3.12).




*Scheme 3.12 (L = $CH_3CN$)*

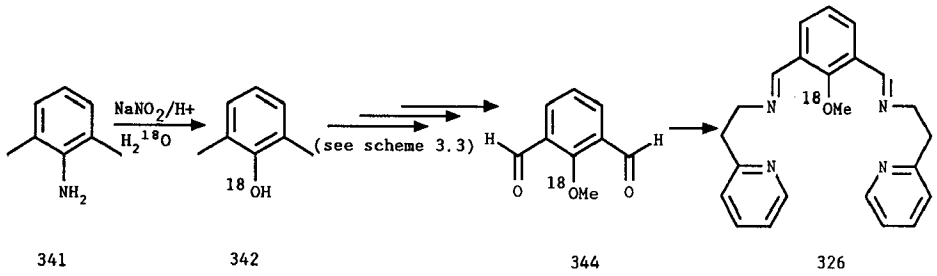
The same product was obtained when 0.5 mmol **332** in 10 ml $CH_2Cl_2/CH_3OH/CH_3CN$ (50 : 10 : 1) was exposed to air for one hour at room temperature. Even when using a mixture of polymeric **333** and $Cu(CH_3CN)_4BF_4$ the same products were obtained after exposure to air for three hours. These findings indicate that a dynamic equilibrium between **330**, **332** and **333** exists in $CH_2Cl_2/CH_3OH/CH_3CN$ mixtures.

An oxygen induced demethylation of the anisole moiety in **330**, **332** and **333** has taken place. In the absence of dioxygen, under an inert atmosphere, these complexes are stable and no trace of demethylation is seen. The phenol ligand **222** could be obtained in 90% yield from complex **221** by an ammonia extraction procedure. This product was identical in all respects with the independently prepared phenol **222** as was described in section 2.6.

In order to obtain further information on the mechanism of this unusual oxidative demethylation and to understand the copper mediated oxygen activation we executed various $^{18}O$ labelling experiments.

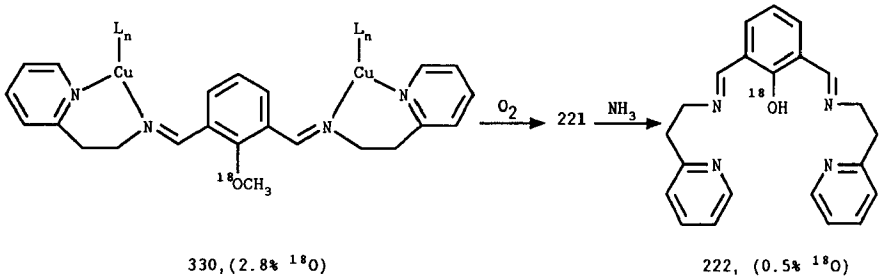
When the oxidation of **330** was carried out in a closed system under similar conditions using $^{18}O_2$ (99.1% enriched) as the oxidant and the oxidation time was prolonged to 24 h., the constitution of the isolated phenol **222** was examined. The phenol obtained in this way was identical to the independently prepared phenol **222** except for the mass analysis. MS spectrometry showed about 60(±5)% $^{18}O$ incorporation into the phenolic group (triplicate experiments). This result indicates at least 60% cleavage of the $C_{arom}$ - O bond. To rule out the possibility of unlabelled $O_2$ leakage in our closed system and subsequent oxidation of the substrate, which could account for the non-labelled product, we prepared the $^{18}O$ enriched ligand **326**. This ligand, exclusively labelled in the ether oxygen, was made by a sequence starting with a diazotization reaction of 2,6-dimethylaniline (**341**) in $^{18}O$ (3% enriched) water, to give $^{18}O$ enriched 2,6-dimethylphenol (**342**), in 33% yield (scheme 3.1). The phenol **342** was converted to 1-methoxybenzene-2,6-dicarboxaldehyde (**344**) using the same sequence as described in section 3.2 except for the

bromination reaction, which was carried out in $CCl_4$ using four equivalents of N-bromosuccinimide and benzoylperoxide (scheme 3.13).




*Scheme 3.13*

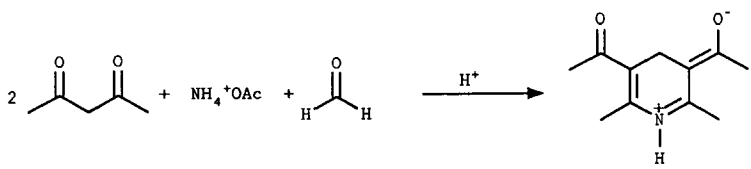
Dialdehyde **344** was identical in all respects to the unlabelled compound **314** except for the mass analysis, which showed a 2.8(±0.3)% $^{18}O$ enrichment. Next **344** was allowed to react with two equivalents of 2-(2-pyridyl)ethylamine (**213**) to give the $^{18}O$ enriched ligand **326**, which was then treated with two equivalents of $Cu(CH_3CN)_4BF_4$ in THF to give the orange precipitate **330**. This precipitate was allowed to react with dioxygen using conditions similar to those described for unlabelled complex **330**. After the oxidation was completed the phenolic ligand was liberated from the complex **221** and analyzed by mass spectrometric methods. This showed an $^{18}O$ enrichment in the phenol of 0.5(±0.3)%. This means a loss of 2.3(±0.3)% $^{18}O$ compared to the starting material **330** (scheme 3.14).




*Scheme 3.14 (L = $CH_3CN$)*

It is not likely that the loss of $^{18}O$ label in **222** is caused by any other (hydrolytic) pathway because aromatic - oxygen bonds are not easily cleaved and certainly not under the mild reaction conditions we employed for the synthesis of these compounds. The presence of $^{18}O$ label in phenol **222**, isolated after the oxidation of **330**, means that at least 20% methyl - oxygen bond cleavage has taken place in this oxidative demethylation reaction.

Next the lost methyl or methoxy substituent was sought. Based on numerous experiments, using various techniques, the liberation of formaldehyde was qualitatively proven, but a quantitative analysis turned out to be extremely difficult in the present system. In most cases traces of formaldehyde were detected using modifications of the method described by Nash[23]. As an example of the use of this method **330** (1 mmol) was dissolved in 10 ml $CH_2Cl_2$ and oxidized with $O_2$ in a closed system at room temperature. After one hour 50 ml diethyl ether was added and the insoluble oxidation products were removed by filtration. The organic layer was stirred vigorously with an aqueous solution of ammonium acetate, acetic acid and acetylacetone for twelve hours (scheme 3.15).




345 346

*Scheme 3.15*

A yellow coloured ether/$H_2O$ mixture appeared. The layers were separated and the 3,5-diacetyl-1,4-dihydrolutidine (**346**) (independently prepared), which has a maximum at 412 nm, could be detected in the water layer using UV techniques thereby indicating the presence of formaldehyde in the oxidation products.

Further analysis of the reaction mixture by GCMS, after oxidation in pure $CH_2Cl_2$, showed the presence of methanol in approximately 30% yield based on starting complex **330**. The yield of methanol could be increased to a maximum of 60% when, after completion of the oxidation, a proton source, e.g. 2,6-dimethylphenol, was added. This probably liberates the methoxy anion from the Cu(II) salts.

Next the origin of the methanol liberated, during this oxidation was investigated. When the oxidation of **330**, 2.8(±0.3)% $^{18}O$ enriched in the methoxy substituent, was performed, 5(±1)% $^{18}O$ incorporation in the liberated $CH_3OH$ was observed (GCMS analysis, duplicate experiments). We made the assumption that $CH_3{}^{18}OH$ and $CH_3OH$ give the same fragmentation patterns in the mass analyzer, which may not be valid. In the reaction of **330** with $^{18}O_2$ (99.1% enriched) as the oxidant no $^{18}O$ incorporation in the liberated $CH_3OH$ was found.

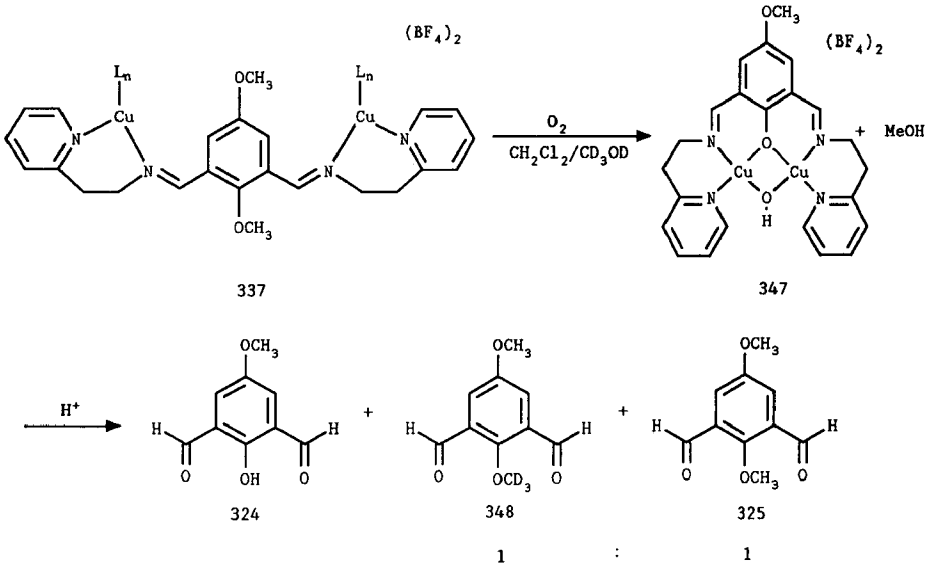
These experiments clearly show that formaldehyde (minor product) and $CH_3OH$ (major product) are formed from ligand **326** via copper induced oxidative demethylation and demethoxylation respectively. The data presented here support dual pathways with at least 60% aryl - oxygen and ≥20% alkyl - oxygen bond cleavage. Both oxidative pathways lead to the same phenoxy-hydroxy bridged dinuclear Cu(II) complex **221**. In the first route an oxidative demethoxylation takes place and $CH_3OH$ is liberated as was detected quantitatively. In the second and minor route oxidative demethylation occurs with the ultimate oxidation of the anisole methyl group to formaldehyde. However, the formation of other products besides formaldehyde and methanol cannot be excluded at present.

### 3.5 *Reaction of $Cu_2$(2,6-BPB-1,4-$OCH_3$)$(BF_4)_2(CH_3CN)_n$ (337) with molecular oxygen*

In order to investigate the role of an electrophilic species in the demethylation and demethoxylation reactions described above, the 4-methoxy

analog **337** of complex **330** was studied. If this reaction proceeds via an electrophilic intermediate, an acceleration of the oxidation of **337** compared to **330** is expected because the *p*-methoxy substituent favours an electrophilic attack at the C-1 position. This would then be in accordance with the electrophilic ($Cu_2O_2^{2+}$) species suggested in related arene hydroxylations by Karlin and co-workers[5a].

Surprisingly a slower replacement of the 1-methoxy substituent took place when **337** was allowed to react with $O_2$ in $CH_2Cl_2$ or a $CH_2Cl_2/CH_3OH$ (40 : 1) mixture. Only 10-30% of the demethylated product **347** was obtained after 1 h. at 25°C, compared to 100% with complex **330** after 1 h.. The extent of demethylation was further established by liberation of the bis-imine ligand and subsequent conversion into the corresponding dialdehyde by acid hydrolysis (scheme 3.16).




*Scheme 3.16 (L = $CH_3CN$)*

If the reaction time was prolonged to 16 h., total demethylation to **347** had taken place (85% isolated yield of **324** after hydrolysis). When this

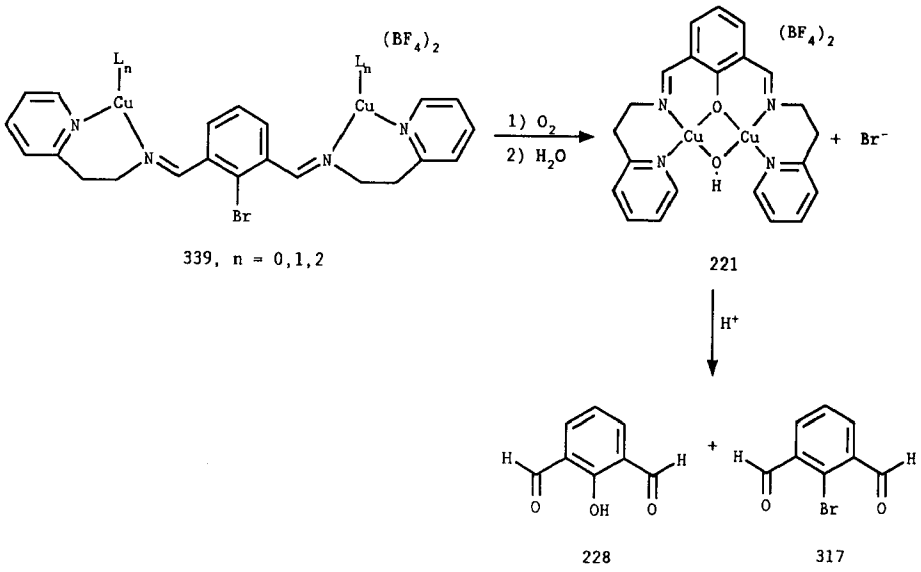
oxidation was carried out in $CH_2Cl_2/CD_3OD$ (40 : 1) for 1 h. at 25°C, analysis of the products, after acid hydrolysis, showed that besides phenol **324** (25%) and dialdehyde **325** (30%), the unexpected dialdehyde **348** (30%) was obtained. In a second experiment with different reaction times and oxidative conversions again equimolar quantities of **325** and **348** were obtained. This means that 50(±2)% $OCH_3$, $OCD_3$ exchange, exclusively at the C-1 position, took place. Control experiments were carried out to establish that the exchange process only occurred in the dinuclear copper(I) complex **337** in the presence of $O_2$ to form the 1-$OCD_3$ isomer of **337**.

The significance of the experimental conditions, namely room temperature and molecular oxygen, needs to be emphasized. In general Lewis acids or HI under rather severe conditions, are required to demethylate methoxy-substituents in aryl compounds. To ensure that the exchange reaction, observed here, is not a simple Lewis acid reaction involving Cu(II) ions, produced from Cu(I) and $O_2$, the experiments were run with ligand **329** in $CH_2Cl_2/CD_3OD$ (40 : 1) in the presence of various Cu(II) salts under otherwise identical conditions. No exchange process was observed, however, within the limits of detection (<2% by $^1H$ NMR).

### 3.6 *Reaction of $Cu_2$(2,6-BPB-1-Br)$(BF_4)_2(CH_3CN)_n$ (339) with molecular oxygen*

When a solution of the 1-bromo complex **339** in $CH_2Cl_2/CH_3OH$ (40 : 1) was allowed to react with molecular oxygen again a rapid colour change from orange to dark green was observed. Isolation and characterization of the oxidation product after 16 h. showed that dinuclear Cu(II) complex **221** had been formed in about 80% yield. Hydrolysis of the reaction mixture, using aqueous HCl, gave the corresponding phenol **228** (yield 80%) together with some unreacted **317** (scheme 3.17).

Analysis of the reaction mixture for $Br^-$ was performed after an aqueous $HNO_3$ (1 N) work up procedure. The separated water layer was titrated with $AgNO_3$ and indeed $Br^-$ inup to 57% recovery could be analyzed



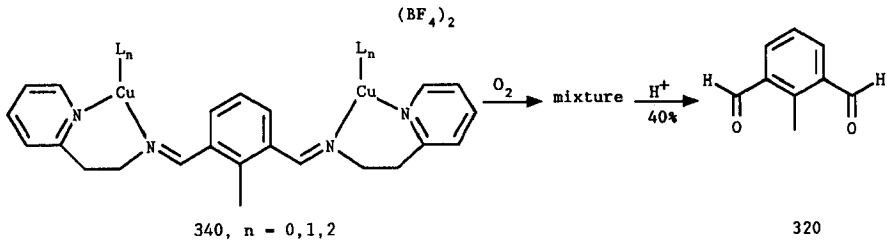

*Scheme 3.17 (L = $CH_3CN$)*

using conductivity measurements. Although we cannot be sure that $Br^-$ is formed directly in the oxygenation reaction, one might suggest that $OBr^-$ will be formed which subsequently decomposes into $Br^-$ and $H_2O$. It is more likely that, analogous to the demethylation reaction of **330** where $^-OCH_3$ is produced, $Br^-$ acts as a leaving group when the C-1 carbon is attacked by a peroxo dicopper(II) species. To our knowledge this reaction represents the first example of a copper-dioxygen induced aryl-debromination reaction.

### 3.7 *Reaction of $Cu_2$(1,3-BPB-2-$CH_3$)$(BF_4)_2(CH_3CN)_n$ (340) with molecular oxygen*

In the previous reactions, characterized by the oxidation of 1-methoxy and 1-bromo substituted dicopper(I) complexes, the C-1 position was blocked with a substituent which could behave as a leaving group ($^-OMe$, $Br^-$) in a nucleophilic substitution like reaction. In our last example a methyl substituent, which is unlikely to behave as a leaving group, was introduced in this position.

When a stirred solution of **340** in a $CH_2Cl_2/CH_3OH/CH_3CN$ (40 : 5 : 1) mixture was exposed to an open air atmosphere and thus allowed to react with dioxygen a colour change from orange to brown-green was observed. After sixteen hours of stirring at room temperature the ligand was isolated by an ammonia extraction procedure (scheme 3.18). In this way a mixture of unidentified compounds was obtained. Mass analysis of this mixture showed a small peak at 372 (ligand + oxygen) but the major $M^+$ peak was observed at 356 (free ligand). Hydrolysis of this mixture by aqueous hydrochloric acid gave only pure 2-methylphenyl-1,3-dicarboxaldehyde (**320**) in 40% yield. No hydroxylation at C-1 was found. This result implies that no oxygenation reaction occurs at the aromatic nucleus when the C-1 position in binuclear complex **340** was blocked with a methyl substituent.




340, n = 0,1,2 320

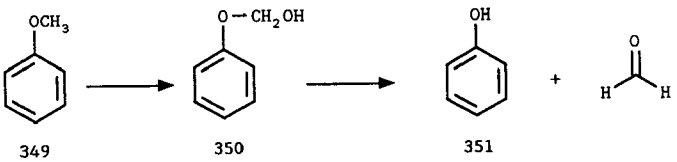
*Scheme 3.18 (L = $CH_3CN$)*

Perhaps a bis($\mu$-hydroxy)dicopper(II) species was formed as was found by Sorrel and co-workers in the reaction of related dinuclear Cu(I) complexes with dioxygen[24]. Alternatively a simple oxidation process might occur in which four Cu(I) ions are oxidized by $O_2$ to form Cu(II) and $H_2O$. An oxygenation at the pyridylethyl part of the ligand system cannot be excluded; the exact nature of this oxidation awaits further study. However, this result seems strange in view of the fact that Karlin and co-workers found a $Cu_2O_2^{2+}$ induced methyl migration in their 1-methyl blocked system[1c] as was described in section 3.1.

In summary we have found that in C-1 methoxy or bromo blocked dinuclear Cu(I) complexes **330**, **337** and **339** a hydroxylation reaction at C-1 occurred when these complexes were exposed to dioxygen, with the resulting loss of $^{-}OCH_3$, $CH_2O$ and $Br^{-}$. When however the C-1 position was blocked with a methyl substituent as in **340**, no (selective) hydroxylation reaction was found. A mechanistic rational for all these observations will be presented in the following section.

### 3.8 *A mechanistic interpretation*

Oxidative demethylation of aryl ethers is catalyzed by various enzymes such as cytochrome P450 dependent monooxygenases, hydroxylases and ligninase[25,26]. Although several pathways have been suggested, the generally accepted mechanism for demethylation, based on cytochrome P450 dependent monooxygenases, involves $\alpha$-hydroxylation to a hemiacetal **350** induced by an iron-oxy species, followed by fragmentation to phenol (**351**) and formaldehyde[27] (scheme 3.19).




349 350 351

*Scheme 3.19 (L = $CH_3CN$)*

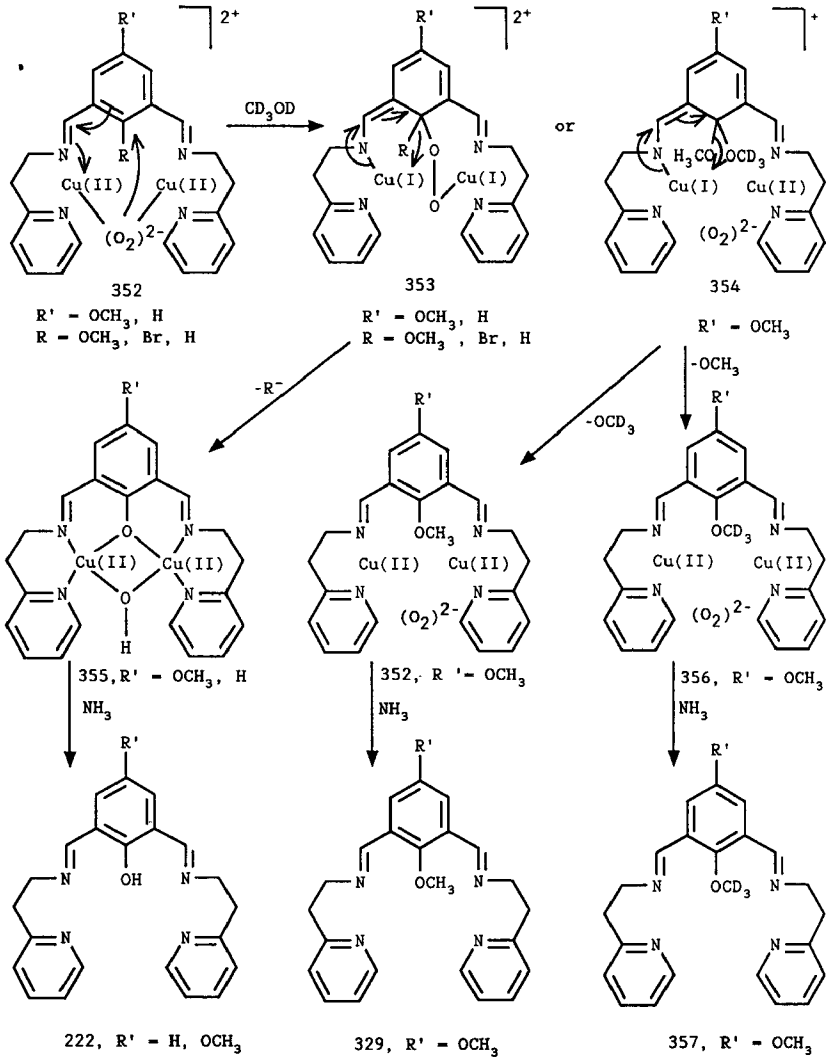
Lindsay Smith and co-workers[22] examined seventeen monooxygenase model systems in the demethylation reaction of anisole. A combination of H/D kinetic isotope effects and $^{18}O$ labelling studies were used. In most model systems the demethylation proceeds by an ipso substitution on the aromatic C-1 carbon atom by an oxy species (e.g. $H_2O$, $Fe^{IV}$-O·, HO·) following different reaction paths to the final products. A few model systems gave both ipso substitution and $\alpha$-hydroxylation and only two model systems, consisting of

iron(III) porphyrines and iodosylbenzene, showed isotope effects comparable with those of the cytochrome P450 dependent monooxygenases. This emphasizes once more the fact that model systems and enzyme mimics can behave very differently from the original enzyme. So one should take great care in extrapolating results found for model systems to real enzymes. No enzymes are known, in which a demethylation takes place induced by a $(Cu_2O_2)^{2+}$ species.

Dehalogenation reactions are catalyzed by various enzymes using hydrolytic, reductive or oxidative pathways[28]. However, few enzymes are able to dehalogenate aromatic compounds by an oxidative process. For instance phenylalanine hydroxylase is able to dehalogenate 4-fluorophenylalanine, using oxygen and some cofactors, to tyrosine[29].

Although we have at present no evidence for the intermediates in the oxidative demethylations and oxidative debromination described here, several mechanistic features might relate to those proposed for $O_2$ binding and arene hydroxylation as described in chapter 2. It is conceivable that in the first instance the reaction of **330**, **337**, **339** and **216** with $O_2$ produces an intermediate dioxygen adduct with proposed structure **352** (a peroxo dicopper(II) complex) (scheme 3.20). The copper ions might coordinate an $CH_3CN$ ligand or employ the $OCH_3$ or Br moiety as a bridging ligand. The reversible binding of $O_2$ in binuclear copper complexes with tetra coordinated copper ions has now good precedent mainly based on the results from Karlin's group[1,30c]. Furthermore the structure of a pentacoordinated $\mu$-1,2-peroxo dicopper(II) complex with distorted trigonal bipyramidal geometry has been obtained[31]. As arene oxygen bond cleavage and methoxide elimination is the preferred pathway in the demethylation of the anisole group in **330** and **337** our data do not seem to support the attack of an electrophilic copper-oxy species to generate, in the first step, an intermediate with an arene-peroxide bond. Karlin and co-workers described related arene hydroxylations as electrophilic in the sense that the arene attacks the peroxo dicopper(II) moiety to generate a cationic arene-peroxide intermediate. The introduction of the

donating $p$-$OCH_3$ substituent as in **337** decreases the rate of the ipso oxygenation reaction and contradicts the electrophilic mode of attack.




*Scheme 3.20: $CH_3CN$ ligands and $BF_4^-$ ions are omitted for sake of clarity*

Although alternative mechanisms for the demethoxylation, debromination and $OCH_3$-$OCD_3$ exchange might be proposed, the mechanism shown in scheme 3.20 accounts for the experimental observations. The increased Lewis acidity upon $O_2$ binding by the binuclear copper centers as present in the peroxo dicopper(II) complex **352**, could result in decreased electron density at the 2,6-bis-imine substituted aryl moiety making it more vulnerable to nucleophilic attack. The effect of the *p*-$OCH_3$ substituent on the oxygenation (slower oxidation) is consistent with this scheme. Detailed knowledge about which step in this process is actually slower awaits full kinetic analysis; preliminary kinetic studies indicate, however, that the binding of $O_2$ to form the peroxo dicopper(II) species is only slightly influenced by the introduction of a para-methoxy-substituent[7] (i.e. complexes **330** vs. **337**). For **352** (R' = $OCH_3$) ipso attack of either the copper(II) peroxy species or deuteromethanol leads to the formation of **353** and acetal intermediate **354**, respectively. In the absence of $CD_3OD$ (or $CH_3OH$) only **353** will be formed as is the case in the demethoxylations in $CH_2Cl_2$. Subsequent fragmentation of **353** results in the formation of **355**. However, fragmentation of acetal intermediate **354** leads to equimolar amounts of **352** (1-$OCH_3$) and **356** (1-$OCD_3$ isomer) respectively. In the oxidation reaction of **330** (1-$OCH_3$) and **339** (1-Br) performed in $CH_2Cl_2/CD_3OD$ (40 : 1) no $OCD_3$ incorporation was observed when the reaction was quenched and the complex hydrolyzed after 10 minutes. Only starting ligands and demethylated or debrominated ligands could be isolated. This indicates a longer lifetime for intermediate **352** (R' = $OCH_3$ than for **352** (R' = H). This allows a more favourable competition between an external nucleophile $HOCD_3$ ($HOCH_3$) and an internal nucleophile (presumably $O_2^{2-}$). If a nucleophilic attack by the aromatic nucleus on an (electrophilic) ($Cu_2O_2^{2+}$) species should occur as suggested in the mechanism proposed by Karlin[1c] one would expect also a nucleophilic attack at $CD_3OD$ to form a deuterated aromatic ring, but no deuterium incorporation was found.

It should be emphasized that data obtained by Solomon, Karlin and co-workers on a phenoxo-bridged dinuclear peroxo Cu(II) complex indicate

either a non-symmetrical $\mu$-1,2-bridged peroxo ligand or a peroxo group bound to a single Cu(II) ion[31]. It is not too farfetched to suggest that similar binding modes, shown schematically in figure 3.5 (structures **358** and **359**), exist in complex **352** ($CH_3CN$ omitted).

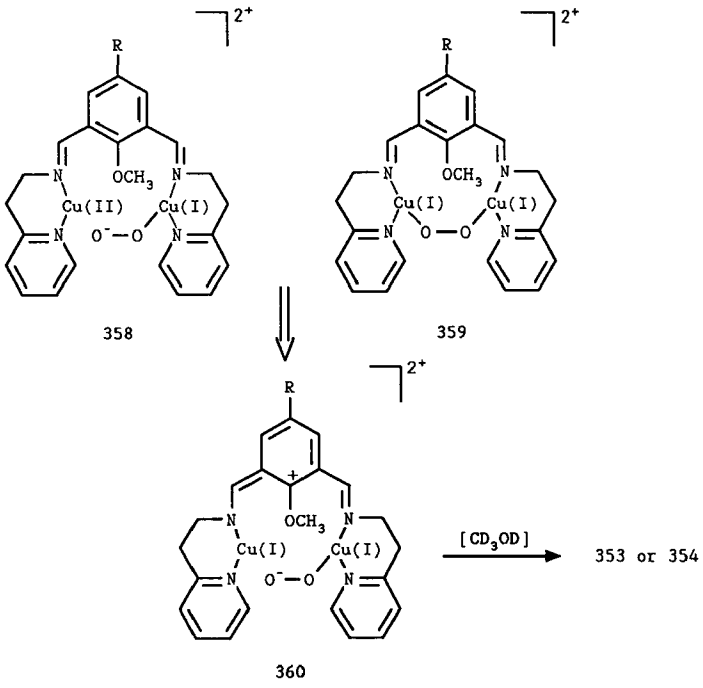



*Figure 3.5*

Considering next complex **360**, which is a resonance structure of **358** and which can be formed from **359** by copper-oxygen bond fission, it is conceivable that ipso attack of the peroxy group or deuteromethanol can be a favourable pathway leading to **353** and **354** respectively. Furthermore protonation of either **358** or **359** by methanol to form copper bound hydroperoxide and methoxide ion adjacent to the arene ring might contribute to the formation of **354**. If **360** makes an important contribution to the overall mechanism it should be noted that this formally means an electron transfer from the arene ring to the peroxo

dicopper moiety[32]. Due to the presence of the imine bonds this does not likely lead to long-lived arene centered radicals, which is consistent with the high selectivity that is observed, although a one electron oxidation by the peroxo dicopper(II) group followed by highly selective radical type conversion cannot be excluded in the specific ligand system present here.

In conclusion, the conversions of **330, 337** and **339** represent, as far as we know, the first examples of an ipso-hydroxylation induced demethylation of aryl ethers and debromination of an aryl bromine using copper ions and $O_2$ under ambient conditions.

For cytochrome P450 dependent monooxygenases the generally accepted mechanism for oxidative O-demethylation involves hydroxylation of the $\alpha$-carbon to give a hemiacetal which subsequently breaks down to a phenol and an aldehyde or ketone[27]. The model systems which mimic these enzymes at best use iron(III)porphyrines and iodosylbenzene[22]. No examples are known in which this process is catalyzed by copper ions and dioxygen.

In tyrosinase, a dicopper oxygen dependent enzyme, it is presumed that the hydroxylation of phenol (to catechol) proceeds via an electrophilic attack of a $(Cu_2O_2)^{2+}$ species at the aromatic ring[2,3]. In the model system of tyrosinase, developed by Karlin and co-workers[8], it is suggested that hydroxylation of the aromatic nucleus also occurs via an electrophilic $(Cu_2O_2)^{2+}$ attack. In our model system however we provided evidence for competing pathways in arylether bond fissions and arene hydroxylations. Our data indicate that formation of an arene-peroxide bond by electrophilic attack[33] on arenes is presumably not an exclusive pathway for these model compounds[34].

### 3.9 *Experimental part*

Mass spectral analyses including high resolution mass spectra and isotope analyses, were carried out on a AEI-MS-902 spectrometer. $^{18}O_2$ oxygen gas (99.10% isotope content) was purchased from Rohstoff Einfuhr. The isotope content was analyzed at regular intervals using high resolution mass spectrometry. For general remarks see chapter 2 section 2.9.

**2,6-($\alpha,\alpha,\alpha',\alpha'$-Tetrabromo-)dimethyl-1-methoxybenzene (313)**

To a stirred solution of 2,6-dimethyl-1-methoxybenzene (**312**) (13.6 g, 0.1 mol) in carbontetrachloride (100 ml) was slowly added bromine (20.5 ml, 0.4 mol) at such a rate that the addition was completed in 3 h. while the solution was continuously irradiated using an IR lamp (Philips 13372 E/06 * OK) and heated just at the reflux temperature. After the addition was completed stirring and irradiation (under reflux) of the solution was continued for 12 h.. The solvent was removed in vacuo and the solid residue crystallized from hexane to furnish **313** as white needles (32.6 g, 72%): m.p. 100.4-102.3°C; $^1$H NMR ($CDCl_3$): $\delta$ 3.90 (s, 3H), 6.95 (s, 2H), 7.08-7.47 (m, 1H), 7.87 (d, $J$ = 8 Hz, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 32.98, 62.49, 126.16, 132.39, 135.32, 147.83 ppm. Analysis calculated for $C_9H_8Br_4O$: C: 23.91, H: 1.77, Br: 70.77, found: C: 23.87, H: 1.84, Br: 70.90.

**1-Methoxybenzene-2,6-dicarboxaldehyde (314)**

A slurry of tetrabromide **313** (5.0 g, 11.0 mmol) in concentrated sulphuric acid (50 ml) was stirred for 36 h. at room temperature. The resulting solution was poured onto crushed ice (100 g) and the aqueous mixture extracted with ether (3 x 50 ml). Drying of the combined ether layers ($MgSO_4$) and concentration afforded a white solid which was crystallized from ether to give **314** as white needles (0.95 g, 53%); m.p. 99.2-100.1°C; $^1$H NMR ($CDCl_3$): $\delta$ 4.07 (s, 3H), 7.26-7.50 (m, 1H), 8.06 (d, $J$ = 8 Hz, 2H), 10.80 (s, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 66.38, 124.52, 129.61, 134.68, 165.01, 187.99 ppm. Analysis calculated for $C_9H_8O_3$: C: 65.85, H: 4.89, found: C: 65.32, H: 4.88. HRMS calculated for $C_9H_8O_3$ 164.047, found 164.048.

The $^{18}$O labelled ligand **344** was prepared by the analogous route, starting with a diazotization of 3.8 g 2,6-dimethylaniline[9] in 10 ml $H_2O$ (3% $^{18}$O enriched) to yield 1.3 g (33%) 2,6-dimethylphenol. Mass analysis of **344** so obtained revealed an enrichment of 2.8(±0.3%) $^{18}$O in **344**.

**2,6-Bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-1-methoxybenzene (326)**

To a stirred solution of dialdehyde **314** (164 mg, 1.0 mmol) in dichloromethane (20 ml) at 20°C was added 2-(2-pyridyl)ethylamine **213** (244 mg, 2.0 mmol). After 60 min., $Na_2SO_4$ (1.0 g) was added, and stirring was continued for 30 min.. The solids were removed by filtration, the filtrate was concentrated to afford the pure bis-imine **326** (340 mg, 91%), yellow oil. $^1$H NMR ($CDCl_3$): $\delta$ 3.17 (t, 4H), 3.54 (s, 3H), 4.10 (t, 4H), 6.80-7.67 (m, 7H), 8.00 (d, $J$ = 8 Hz, 2H), 8.50 (br s, 4H); $^1$H NMR ($d_6$-DMSO): $\delta$ 3.07 (t, 4H), 3.52 (s, 3H), 3.97 (t, 4H), 7.12-7.28 (m, 3H), 7.40-7.48 (m, 2H), 7.89 (d, 2H), 8.45 (s, 2H), 8.48 (d, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 39.15, 61.11, 63.77, 120.85, 123.37, 124.25, 129.11, 129.54, 135.80, 148.92, 156.55, 159.34; $^{13}$C NMR ($d_6$-DMSO): $\delta$ 38.83, 60.51, 64.13, 121.28, 123.41, 124.42, 129.24,

129.33, 136.19, 148.94, 155.93, 159.29, 159.32. HRMS calculated for $C_{23}H_{24}N_4O$: 372.191, found 372.190.

**2,6-($\alpha,\alpha,\alpha',\alpha'$-Tetrabromo)-1-bromobenzene (316)**

To a solution of 9.25 g (50 mmol) of 2,6-dimethyl-1-bromobenzene (**315**) in 150 ml $CCl_4$, heated under reflux and under continuous irradiation with an IR-photolamp was slowly added over an 1 h. period, 32 g (0.2 mol) of bromine. After the addition was completed the resulting mixture was heated and irradiated for an additional 12 h.. By that time the bromine had completely disappeared. The solvent was removed in vacuo and the residue purified by crystallization from $CHCl_3$ affording **316** as a white crystalline material; yield 21.0 g (84%); m.p. 152.4 - 153.2°C; $^1$H NMR ($CDCl_3$): $\delta$ 7.13 (s, 2H), 7.51 (m, 1H), 8.06 (d, $J$ = 8 Hz, 2H). Analysis calculated for $C_8H_5Br_5$: C: 19.16, H: 1.01, Br: 79.84, found C: 19.28, H: 1.08, Br: 80.02. HRMS calculated for $C_8H_5Br_5$: 495.631, found 495.630.

**1-Bromobenzene-2,6-dicarboxaldehyde (317)**

A slurry of 5.0 g (10 mmol) finely powdered **316** was heated at 60°C in 50 ml concentrated $H_2SO_4$ for 24 h. After the solution was cooled to 25°C it was poured onto 200 g crushed ice. The white precipitate was filtered, dried over $MgSO_4$ and crystallized from ether/$CHCl_3$ to yield 1.8 g (85%) white crystalline material. m.p. 140.0-141.1°C; $^1$H NMR($CDCl_3$): $\delta$ 7.54 (m, 1H), 8.13 (d, $J$ = 8 Hz, 2H), 10.53 (s, 2H). Analysis calculated for $C_8H_5BrO_2$: C: 45.07, H: 2.34, Br: 37.56, found C: 44.87, H: 2.49, Br: 37.49. HRMS calculated for $C_8H_5BrO_2$: 211.947, found 211.946.

**2,6-Bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-1-bromobenzene (327)**

Dialdehyde **317** (213 mg, 1 mmol) was converted into the bis-imine **327** following the procedure as described for **326**. Yield 390 mg (93%) of **327** as a colourless oil which was pure according to $^1$H and $^{13}$C NMR. $^1$H NMR($CDCl_3$): $\delta$ 3.15 (t, $J$ = 7 Hz, 4H), 4.04 (t, $J$ = 7 Hz, 4H), 7.10 (m, 4H), 7.26 (t, $J$ = 7.8 Hz, 1H), 7.52 (m, 2H), 7.91 (d, $J$ = 7.3 Hz, 2H), 8.50 (d, $J$ = 5.1 Hz, 2H), 8.57 (s, 2H). $^{13}$C NMR($CDCl_3$): $\delta$ 39.19, 60.83, 121.14, 123.52, 126.63, 127.24, 130.51, 135.08, 136.09, 149.12, 159.29, 160.24. HRMS calculated for $C_{22}H_{21}BrN_4$: 420.095, found: 420.093.

**2,6-Dicyanotoluene (319)**

A mixture of 16.1 g (0.1 mol) 2,6-dichlorotoluene (**318**), 21.8 g (0.24 mol) dry CuCN and 17 ml pyridine is heated under reflux with the aid of a metal bath at 250-260°C for 60 h. under a $N_2$ atmosphere. Then the temperature of the mixture is lowered to ±100°C and the contents are poured into a beaker containing a mixture of 200 ml concentrated ammonia/$H_2O$

(1 : 1). The mixture was stirred vigorously for 15 minutes. Subsequently 200 ml ether was added and stirring was continued for 10 minutes. After filtration, to remove the insoluble material, the layers were separated. The water layer was washed with ether (2 x 50 ml). The combined ether layers were washed successively with concentrated ammonia (2 x 50 ml) and 4 N HCl (2 x 50 ml). After drying and evaporation in vacuo a yellow material was obtained, which was crystallized from hexane/$CHCl_3$ to yield 4.5 g (32%) of yellow crystalline dinitrile **319**. m.p. 132.9-133.8°C; $^1$H NMR($CDCl_3$): $\delta$ 2.73 (s, 3H), 7.16-7.52 (m, 1H), 7.83 (d, $J$ = 8 Hz, 2H); $^{13}$C NMR($CDCl_3$): $\delta$ 19.38, 114.68, 116.10, 127.04, 136.24, 145.47. Analysis calculated for $C_9H_6N_2$: C: 76.04, H: 4.22, N: 19.69, found: C: 75.98, H: 4.35, N: 19.43. HRMS calculated for $C_9H_6N_2$: 142.053, found: 142.052.

**Toluene-2,6-dicarboxaldehyde (320)**

To a solution of 1.42 g (10 mmol) 2,6-dicyanotoluene (**319**) in 50 ml toluene was slowly added at room temperature, 22 ml (22 mmol) of a 1.0 M solution of DIBAL-H in toluene in 15 minutes giving a yellow coloured solution. After 2 h. of stirring at room temperature, 10 ml of a $H_2O/CH_3OH$ mixture was carefully added at such a rate that the solution did not boil. Next 15 ml of 4 N HCl was slowly added (caution!, this is a very exothermic process) and stirring was continued for 15 minutes. The layers were separated and the water layer was washed with ether (2 x 50 ml). The combined ether layers were dried over $MgSO_4$ and solvent evaporation in vacuo afforded white crystalline material which was recrystallized from hexane to yield 840 mg (56%) of **320** as white needles. m.p. 101.7-102.3°C; $^1$H NMR($CDCl_3$): $\delta$ 2.97 (s, 3H), 7.50 (t, 1H), 8.03 (d, $J$ = 7.6 Hz, 2H), 104.0 (s, 2H); $^{13}$C NMR($CDCl_3$): $\delta$ 13.39, 126.51, 135.30, 136.18, 142.50, 191.38. Analysis calculated for $C_9H_8O_2$: C: 72.89, H: 5.44, found C: 72.20, H: 5.44. HRMS calculated for $C_9H_8O_2$: 148.052, found 148.051.

**1,3-Bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-2-methylbenzene (328)**

This compound was made following the same procedure as used for **326** Starting from 148 mg (1 mmol) **320** and 244 mg (2 mmol) **213**, 343 mg (96%) of a colourless oil was obtained, which was pure **328** according to $^1$H and $^{13}$C NMR. $^1$H NMR($CDCl_3$): $\delta$ 2.29 (s, 3H), 3.16 (t, $J$ = 6.7 Hz, 4H), 4.01 (t, $J$ = 7.0 Hz, 4H), 7.04-7.24 (m, 5H), 7.53 (t, 2H), 7.78 (d, $J$ = 7.2 Hz, 2H), 8.49 (s, 2H), 8.52 (d, 2H); $^{13}$C NMR($CDCl_3$): $\delta$ 13.77, 39.42, 61.42, 121.12, 123.71, 125.91, 129.34, 134.94, 136.06, 136.22, 149.16, 159.56, 160.21. HRMS calculated for $C_{23}H_{24}N_4$: 356.200, found 356.202.

**$\alpha^2,\alpha^6$-Dibromo-2,6-dimethyl-4-methoxyphenol (323)**

This compound was prepared in two steps following the procedures described in reference 10, (overall yield 60%), m.p. 112.1-113.6°C (lit. 113-114°C).

**1-Hydroxy-4-methoxybenzene-2,6-dicarboxaldehyde (324)**

A stirred mixture of $\alpha^2,\alpha^6$-dibromo-2,6-dimethyl-4-methoxyphenol (**323**) (10.0 g, 32 mmol), aqueous acetic acid (50% HOAc, 150 ml) and hexamethylenetetramine (15.0 g, 107 mmol) was heated at reflux for 2.5 h.. After this period concentrated HCl (25 ml) was added and reflux was continued for 15 min. The red aqueous acetic acid solution was cooled to room temperature and extracted with ether (3 x 100 ml). After separation, the organic layers were washed with water (3 x 25 ml), dried ($MgSO_4$) and concentrated. The yellow residue was crystallized from ethyl acetate to furnish dialdehyde **324** (1.99 g, 33%) as yellow needles: m.p. 121.5-123.4°C; $^1$H NMR ($CDCl_3$): $\delta$ 3.85 (s, 3H), 7.52 (s, 2H), 10.20 (s, 2H), 11.17 (s, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 56.00, 122.23, 123.33, 152,42, 157,73, 191.58 ppm. Analysis calculated for $C_9H_8O_4$: C: 60.05, H: 4.44, found: C: 60.12, H: 4.54.

**1,4-Dimethoxybenzene-2,6-dicarboxaldehyde (325)**

A solution of phenol **324** (100 mg, 0.56 mmol), $Ba(OH)_2 \cdot H_2O$ (95 mg, 0.56 mmol) and methyliodide (0.1 ml) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 16 h.. The resulting mixture was poured into water (50 ml) and extracted with ether (3 x 30 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The solid residue was crystallized from ether to provide **325** (60 mg, 55%) as yellow-orange needles: m.p. 110.5-112.8°C; $^1$H NMR ($CDCl_3$): $\delta$ 3.87 (s, 3H), 4.03 (s, 3H), 7.63 (s, 2H), 10.50 (s, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 55.91, 66.93, 119.22, 130.72, 156.19, 159.40, 188.02 ppm. Analysis calculated for $C_{10}H_{10}O_4$: C: 61.85, H: 5.19, found: C: 61.73, H: 5.15. HRMS calculated for $C_{10}H_{10}O_4$: 194.04, found 194.05.

**2,6-Bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-1,4-dimethoxybenzene (329)**

Dialdehyde **325** (124 mg, 0.64 mmol), was converted, following the same procedure as for **326**, into the pure bis-imine **329** (240 mg, 93%), yellow oil. $^1$H NMR ($CDCl_3$): $\delta$ 3.23 (t, 4H), 3.55 (s, 3H), 3.86 (s, 3H), 4.10 (t, 4H), 6.95-7.81 (m, 8H), 7.60 (s, 2H), 8.50 (s, 2H), 8.63 (s, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 38.91, 55.18, 60.83, 63.88, 114.06, 120.71, 123.21, 129.62, 135.66, 148.67, 153.43, 155.44, 156.24, 159.07 ppm. HRMS calculated for $C_{24}H_{26}N_4O_2$: 402.206, found 402.204.

**(2,6-Bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-1-methoxybenzene)tetra(acetonitrile)biscopper(I) bis(tetrafluoroborate) $Cu_2(2,6\text{-BPB-1-OCH}_3)(CH_3CN)_4(BF_4)_2$ (330)**

A solution of **326** (240 mg, 0.65 mmol) in tetrahydrofuran (10 ml) was added to a suspension of $Cu(CH_3CN)_4BF_4$ (**215**) (410 mg, 1.3 mmol) in tetrahydrofuran (10 ml). The mixture was stirred vigorously for 16 h. during which period an orange precipitate was formed. The product was isolated by filtration, washed with tetrahydrofuran and dried in vacuo to afford bis Cu(I) complex **330** (480 mg, 90%), orange powder. $^1$H NMR ($d_6$-DMSO): $\delta$ 2.08 (s, 12H), 3.20 (m, 4H), 3.74 (s, 3H), 4.14 (m, 4H), 7.18-7.53 (m, 5H), 7.85 (m, 2H), 8.35 (s, 4H), 8.75 (s, 2H). Analysis calculated for $C_{31}H_{36}B_2Cu_2F_8N_8O$: C: 45.40, H: 4.58, Cu: 14.55, N: 12.83, found: C: 44.63, H: 4.49, Cu: 14.52, N: 12.59. IR (KBr): 2255 (w), 1600, 760 $cm^{-1}$. Several attempts to crystallize **330** from THF, $CH_3OH$, $CH_2Cl_2$, $CH_3CN$ and mixtures of these solvents failed to yield crystals of sufficient quality for an X-ray determination.

**2,6-Bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-1-methoxybenzene)biscopper(I)bis(tetrafluoroborate) $Cu_2(2,6\text{-BPB-1-OCH}_3)(BF_4)_2CH_2Cl_2)_{0.50}$ (332)**

To the orange precipitate of **330**, prepared from **326** (240 mg, 0.65 mmol) as described above was added, after filtration and washing with tetrahydrofuran, dichloromethane (10 ml). The orange mixture was stirred and heated at reflux for 0.5 h.. During dissolution of the orange material a white solid appeared, which was separated after cooling, from the colourless solution by filtration. After washing with dichloromethane and methanol and drying in vacuo there was obtained $Cu_2(1,3\text{-BPB-2-OCH}_3)(BF_4)_2$ (**332**) (250 mg, 58%) as a white powder. $^1$H NMR ($d_6$-DMSO): $\delta$ 3.18 (br s, 4H), 3.75 (s, 3H), 4.12 (br s, 4H), 7.30 (s, 2H), 7.44 (d, 2H), 7.50 (br s, 1H), 7.82 (m, 2H), 8.28 (br s, 4H), 8.71 (br s, 2H); $^{13}$C NMR ($d_6$-DMSO): $\delta$ 36.30, 60.35, 64.47, 122.61, 122.67, 123.07, 124.56, 127.71, 130.33, 137.90, 148.80, 159.39, 159.81 ppm. Analysis calculated for 0.5 dichloromethane solvate $C_{23.5}H_{25}B_2ClCu_2F_8N_4O$: C: 39.44, H: 3.52, Cl: 4.95, Cu: 17.76, F: 21.24, N: 7.83, found: C: 38.78, H: 3.49, Cl: 4.79, Cu: 17.71, F: 21.28, N: 7.84.

When complex **332** (0.5 mmol) was dissolved in $CH_2Cl_2$ and 4 equivalents of $CH_3CN$ were added the orange colour indicating the presence of **330** reappeared. Stirring for 2 h. at room temperature was followed by concentration and work-up as described for the preparation of **330**. After washing (THF) and drying in vacuo bis-Cu(II) complex **330** (80-90%) was obtained, in all respects identical with **330** prepared as described above. The conversion of **330** to **332** and vice versa could be repeated several times with small (10-20%) loss of material.

When a solution of complex **332** in $CHCl_3/CH_3CN$ (10 : 1 ratio) was crystallized very slowly at room temperature both orange and white crystalline material was obtained in 1 : 1 ($\pm$0.1) molar ratio. The crystals were separated manually. The white material was found to be $Cu(CH_3CN)_4BF_4$ (**215**) (X-ray determined).

Crystals suitable for X-ray analysis were obtained from the orange material. This appeared to be a linear copper(I) coordination polymer.

**Crystal structure determination of coordination polymer 333**

The single crystal X-ray determination was performed at 130K with MoK$\alpha$ radiation ($\lambda$ = 0.71073 Å) on a Nonius CAD4F-diffractometer equipped with a graphite monochromator and interphased to a PDP 11/23 using a scan rate of 2° (in omega) and a scan width of 0.7 + 0.35 tg$\Theta$. A crystal of dimensions 0.30 x 0.25 x 0.20 mm was obtained by crystallization from $CHCl_3/CH_3CN$ and crystallized in the monoclinic space group $P2_1/n$ with a = 13.826(3), b = 9.938(2), c = 20.555(6) Å, $\beta$ = 102.58 °(z), and V = 2756.5 $Å_3$. For Z = 4 and F.W = 642.20 the calculated density is 1.55 $gcm^{-3}$. For $1° \leq \Theta \leq 27°$ 5563 reflections were obtained, 3618 had reflections with $I \geq 3\sigma(I)$ and were only used in the refinements. The structure was partly solved by direct methods. The remaining atoms, including all the H-atoms were located in succeeding difference Fourier synthesis. Block-diagonal least squares of F, with unit weights, converted to a final R = 0.059 and R = 0.065 respectively, using anisotropic thermal parameters for the non H-atoms and isotropic fixed thermal parameters (B = 5 $Å^2$) for the H-atoms. In the refinement the H atoms were constraint to their corresponding C-atoms at a distance of 0.95 Å.

**(2,6-Bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-1-bromobenzene)biscopper(I)bisacetonitrile bis(tetrafluoroborate) $Cu_2$(2,6-BPB-1-Br)$(BF_4)_2(CH_3CN)_2$ (339)**

This compound was prepared following the same procedure as was described for **330**. Ligand **327** (421 mg, 1 mmol) was reacted with two equivalents $Cu(CH_3CN)_4BF_4$ (628 mg, 2 mmol) to yield an orange powder (708 mg, 88%) which was washed three times with 10 ml THF. Analysis calculated for $C_{26}H_{27}B_2BrCu_2F_8N_6$: C: 38.82, H: 3.36, Br: 9.95, Cu: 15.80, N: 10.45, found C: 37.72, H: 3.45, Br: 9.91, Cu: 16.10, N: 10.10. (This complex slowly loses weight when stored, probably due to evaporation of acetonitrile)

**(1,3-Bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-2-methylbenzene)biscopper(I)bis(tetrafluoroborate) $Cu_2$(1,3-BPB-2$CH_3$)$(BF_4)_2$ (340)**

This complex was prepared following the same procedure as was described for **332**. Ligand **328** (356 mg, 1 mmol) was reacted with $Cu(CH_3CN)_4BF_4$ (628 mg, 2 mmol) to yield after boiling in $CH_2Cl_2$ a white powder (430 mg, 65%) which was not further purified. Analysis calculated for $C_{23}H_{24}N_4Cu_2B_2F_8$: C: 42.03, H: 3.68, N: 8.53, Cu: 19.36, found: C: 41.99, H: 3.69, N: 8.46, Cu: 19.14.

**(2,6-Bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-1,4-dimethoxybenzene)biscopper(I) bis(tetrafluoroborate) $Cu_2$(2,6-BPB-1,4-$OCH_3$) ($BF_4$)$_2$ (338)**

Bis copper(I) complexes **337** and **338** were prepared from 2,6-bis-[N-(2-(2-pyridyl)ethyl) formidoyl]-1,4-dimethoxybenzene following the same procedures as described for **330** and **332**. Thus starting with **329** (202 mg, 0.5 mmol) and $Cu(CH_3CN)_4BF_4$ (**215**, 314 mg, 1.0 mmol) the binuclear copper(I) complex **337** (350 mg, 80%) was obtained as an orange powder.

Elemental analysis gave a ratio Cu : N = 1 : 3.6 indicating a mixture of complexes with two and four $CH_3CN$ ligands coordinated. Unfortunately no satisfactory analysis for the tetra-acetonitrile coordinated complex **337** was obtained.

Pure binuclear complex **338** (210 mg, 60%) was isolated as a white powder following the procedure of boiling of **337** (0.5 mmol) in $CH_2Cl_2$ (1 h.), washing with $CH_3OH$ and drying in vacuo. Analysis calculated for $C_{24}H_{26}Cu_2F_8N_4O_2$: C: 40.99, H: 3.73, Cu: 18.07, N: 7.96, found: C: 40.93, H: 3.81, Cu: 18.11, N: 7.77.

Acetonitrile complexation and decomplexation experiments with **337** and **338** were executed as described for **330** and **332**.

**2,6-Bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-1-hydroxybenzenebiscopper(II)-hydroxy bis(tetrafluoroborate)monohydrate $Cu_2$(2,6-BPB-1-O)(OH)($BF_4$)$_2 \cdot H_2O$ (221)**

Through a solution of 200 mg (0.23 mmol) (**330**) in 10 ml $CH_2Cl_2$ or a solution of **332** in $CH_2Cl_2/CH_3CN$ at room temperature was bubbled oxygen. The colour of the orange solution rapidly turned dark-green. After one hour the reaction was completed and $CH_3OH$ (10 ml) was added. The dark-green solution was evaporated to dryness and the solid residue was crystallized from $C_2H_5OH/H_2O$ (10 : 1) yielding dark-blue green crystals of **221** (150 mg, 95%), which were suitable for X-ray analysis (see also chapter 2). Analysis calculated for $C_{22}H_{22}B_2Cu_2F_8N_4O_2 \cdot H_2O$: C: 38.12, H: 3.49, Cu: 18.34, F: 21.92, N: 8.08, found: C: 38.13, H: 3.56, Cu: 18.17, F: 22.16, N: 8.03.

**$^{18}$O-Labelling experiments**

Following the same procedure, but using a closed system, 100 mg (0.12 mmol) of **330** dissolved in 20 ml $CH_2Cl_2$ was oxidized using excess $^{18}O_2$ (99.1% enriched). After stirring for 24 h. at room temperature the reaction mixture, a green slurry, was quenched with oxygen free aqueous ammonia (10 ml). The $CH_2Cl_2$ layer was separated and washed again with 10 ml aqueous ammonia. After drying over $Na_2SO_4$ and evaporation to dryness a yellow oil (39 mg, 90%) was isolated. This compound was identical to **222** in all respects except for the mass spectral analysis. MS ($M^+$ at m/e 358, 360) revealed a 55-65(± 5)% $^{18}$O incorporation in the ligand (triplicate experiments). $^{18}$O-labelled complex **330** was prepared following exactly the

procedures for unlabelled **330** from **344** (2.8(±0.3)% $^{18}O$ enriched), **213** and $Cu(CH_3CN)_4BF_4$. The oxidation of $^{18}O$-labelled **330** (0.1 mmol) was performed with $O_2$ under the same conditions as described above and the resulting complex **222** converted into **19** using the ammonia extraction procedure. The oil (90-95%) thus obtained was identical in all respects with **222** made independently except for the MS spectrum. Mass spectral analysis ($M^+$ at m/e 358, 360) indicated 0.5(±0.2)% $^{18}O$ enrichment in the phenol **222** (duplicate experiments).
When a solution of 100 mg (0.12 mmol) **330** in 10 ml highly purified $CH_2Cl_2$ was oxidized in a closed system for 1 h. and the resulting solution analyzed by GC using benzene as an internal standard methanol up to 0.03 mmol could be detected. When however 60 mg 2,6-dimethylphenol (0.5 mmol) was added after 1 h. of oxidation and stirring was continued for an additional 5 min. upto 0.07 mmol (60%) methanol was obtained (GCMS) (duplicate experiments). When **330**, prepared from $^{18}O$ enriched (2.8(±0.3)%) **344**, was used in the same procedure, GCMS analysis of the resulting solution showed an incorporation of $^{18}O$ (5(±1)%) in the methanol. Finally when the oxidation of **330** with $^{18}O_2$ (99.1% enriched) was performed as described above and the liberated methanol analyzed by GCMS no incorporation of $^{18}O$ in the $CH_3OH$ could be detected (triplicate experiments).

**Oxidation of $Cu_2$(2,6-BPB-1-Br)$(CH_3CN)_2(BF_4)_2$ (339)**

A solution of 300 mg (0.38 mmol) **339** in 10 ml $CH_2Cl_2/CH_3OH$ (10:1) was stirred for 24 h. at room temperature under an atmosphere open to the air. A rapid colour change from orange to dark green was observed. Next 10 ml aquabidest and 1 ml concentrated $HNO_3$ was added. Shaking of the mixture for 5 minutes hydrolyzed the bis-imine to the free dialdehyde. The $CH_2Cl_2$ layer was separated, dried over $MgSO_4$ and evaporated to dryness. Analysis of the product by $^1H$ NMR showed that 80(±10)% 1-hydroxybenzene-2,6-dicarboxaldehyde (**228**) had been formed, while 20(±10)% of the starting 1-bromobenzene-2,6-dicarboxaldehyde (**317**) was recovered based on $^1H$ NMR. Next the water layer was analyzed for bromine. All $CH_2Cl_2$ was removed by centrifugation. From the resulting water layer (30 ml) 2 ml was separated and diluted to 30 ml. This was then titrated with a 0.01 N $AgNO_3$ solution following the titration potentiometric; 1.81 ml $AgNO_3$ solution was necessary to reach the point of equivalence. This meant that 21.7 mg $Br^-$ (57% based on the expected quantity) was present in the water layer from the hydrolysis reaction of the oxidation product.

**Oxidation of $Cu_2$(1,3-BPB-2-Me)$(BF_4)_2$ (340)**

A solution of 250 mg (0.4 mmol) dinuclear copper(I) complex **340** in 10 ml of a $CH_2Cl_2/CH_3OH/CH_3CN$ (40 : 5 : 1) mixture was stirred for 24 h. at room temperature under an open atmosphere. A colour change from orange to brown-green was observed. Next, this solution was extracted twice with 10 ml ammonia and once with 10 ml $H_2O$ and subsequently

dried over $Na_2SO_4$. Evaporation of the solvents yielded 130 mg of a dark brown oily residue. $^1H$ NMR and $^{13}C$ NMR showed that this was a mixture of several products, which could not be separated. Mass analysis revealed a peak at 356 (free ligand **328**) and a small peak at **372** (ligand + oxygen?). Hydrolysis of this oil was performed by dissolving it in 30 ml $CH_2Cl_2$ and subsequently washing the methylene-chloride solution with 1 N HCl (2 x 30 ml). Drying of the $CH_2Cl_2$ layer on $MgSO_4$ and evaporation to dryness yielded only 20 mg (37%) of starting methylaldehyde **320** which was pure according to $^1H$ NMR.

**Oxidation of 337 in $CH_2Cl_2/CD_3OD$ mixtures, Typical procedure**

Dry air (or $O_2$ gas) was bubbled through a solution of complex **337** (0.2 g, 0.26 mmol) in a mixture of $CH_2Cl_2/CD_3OD$ (40 : 1 ratio) at room temperature while the solution was continuously stirred. A rapid colour change from orange to dark green was observed. After 1 h. the reaction mixture was poured into a cold aqueous 2 N HCl solution (10 ml). The dichloromethane layer was separated and the aqueous layer extracted with $CH_2Cl_2$ (15 ml). After drying ($MgSO_4$) of the $CH_2Cl_2$ solution and evaporation of the solvent a colourless solid material (45 mg, approx. 90%) was obtained. $^1H$ NMR analysis ($CDCl_3$) showed that this material consists of a mixture of **324** and **348** + **325** (3 : 7 ratio). This mixture was dissolved in $CH_2Cl_2$ (30 ml) and the solution subsequently washed with 1 N aqueous NaOH (2 x 10 ml). Drying of the organic solution ($MgSO_4$) and removal of the solvent in vacuo yielded 32 mg of a solid consisting of **325** and **348** (1 : 1 ($\pm$0.06) ratio) based on $^1H$ NMR and GCMS analysis.

Compounds **325** and **348** were in all respects identical with independently prepared sample (see above); **348**: $^1H$ NMR ($CDCl_3$): $\delta$ 3.82 (s, 3H), 7.54 (s, 2H), 10.32 (s, 2H), MS m/e at $M^+$ = 197; for the **325**, **348** mixture: MS m/e at $M^+$ = 194, 197 (1 : 1 ratio).

The oxidation experiment was repeated several times with different solvent ratio's and reaction times. The ratio **324** to **325** + **348** increased with prolonged reaction times, the ratio **325/348** was 1 : 1 within the limits of detection in all cases.

Various control experiments were performed under the conditions described above, for instance using either ligand **329** and 2 equivalents of copper(II) salts or using **329** under oxygen free conditions. No trace of **324** or **348** was obtained however.

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# CHAPTER 4

## SYNTHESIS AND REACTIVITY OF A DINUCLEAR *p*-HYDROQUINONE-COPPER(II) COMPLEX

### 4.1 *Introduction*

Currently much effort is being devoted to the development of useful catalytic systems for mild and selective oxidations with the aid of molecular oxygen[1]. Furthermore it is of great interest to elucidate the factors that determine the (reversible) binding and activation of $O_2$ in various natural oxygen transport systems and mono- and dioxygenases and to mimic their activity[2]. Guided by nature, intriguing model systems[3] for copper-containing enzymes such as hemocyanin[2,4] have been developed. Considerable progress has been made to establish the active species in cytochrome P450 and related oxygenases[5] as was described in chapter 2. Unlike the successful development of oxidation catalysts based on metalloporphyrins[6], examples of synthetically useful catalysts based on copper complexes that act as mimics for copper containing monooxygenases (e.g. tyrosinase and dopamine-ß-hydroxylase[7,8]) are scarce. This is even more surprising if one realizes that selective oxidations of organic substrates mediated by copper-amine complexes have been known for over a century[1,9,10,11]. The Glaser oxidative coupling of acetylenes[11], the oxidative dimerization of naphthols as observed by Havinga and Brackman[12] and the formation of polyphenylene ethers from 2,6-disubstituted phenols as discovered by Hay[13] are all based on copper-amine complexes and molecular oxygen. Numerous studies have dealt with these oxidations[10] and useful extensions to $\gamma$-oxidation of enones[14], asymmetric phenol oxidations[15], cis,cis-muconic acid synthesis[16] as well as improvements on poly-1,4-phenylene ether formation have been found[10,17]. Stoichiometric arene hydroxylation has been

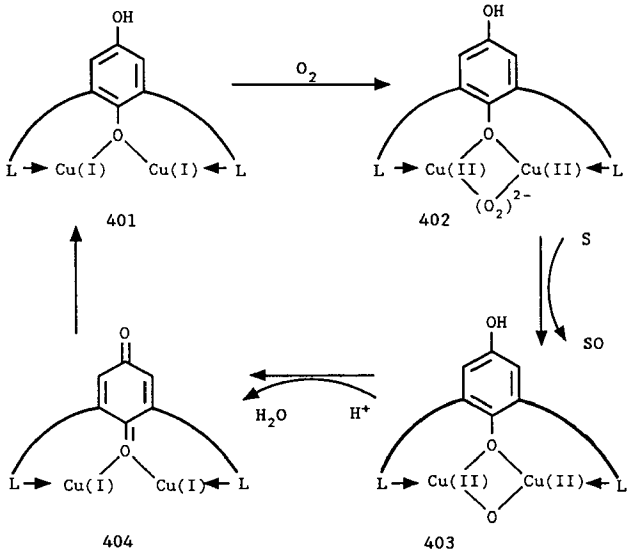
observed[18,19] during studies of the reactivity of $O_2$ at copper centers in dinuclear complexes designed to mimic certain oxygenases. Furthermore catalytic dehydrogenations[19,20] and phosphine and sulfide oxidations[21] have been reported.

In chapter 2 and 3 we described new model systems for the active site of certain monooxygenases, such as tyrosinase. However, oxygen was only incorporated stoichiometrically into the ligands that were used in these copper complexes. We did not succeed in developing an oxidation catalyst whereby oxygen is incorporated into external substrates in a catalytic manner.

Two approaches for the successful development of a selective oxidation catalyst can be followed: 1. Incorporation of one oxygen atom of $O_2$ into the substrate[1,23], as in tyrosinases. These monooxygenases[2,24], with two copper ions in the active center, catalyze the incorporation of one oxygen atom into the ortho-position of phenols; an external electron- and proton-source is required to convert the second oxygen atom into water. In cytochrome P450 based metalloporphyrin catalysts,[5,6] this problem is circumvented by either the use of "single-oxygen" donors[6,25] or by using an external reducing agent[6,26]. 2. Both oxygen atoms of $O_2$ are used for substrate oxidation as is the case with dioxygenases[1,23]. Groves and Quinn[27] have devised an elegant system for oxygen-oxygen bond fission and aerobic epoxidation based on sterically hindered ruthenium porphyrins.

In the approach described in this chapter, a copper(I) - copper(II) redox couple and a hydroquinone-quinone redox couple are incorporated in one catalytically active complex as is shown in scheme 4.1.

The intention is to activate molecular oxygen either as superoxo or $\mu$-peroxo via electron transfer from the Cu(I) dinuclear system. In the previous two chapters we have shown that this $\mu$-peroxo-dicopper(II) species as present in **402**, is a powerful oxidizing agent, giving an internal hydroxylation of the aromatic nucleus. In the present approach, however, the aromatic nucleus is already hydroxylated, therefore we expect a different reaction path, for example, an external substrate may be oxidized. This event then leads to a

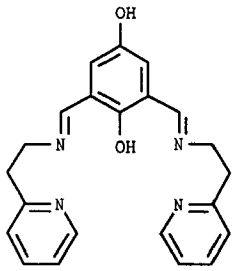



*Scheme 4.1*

hydroquinone, and hydroxy bridged dinuclear Cu(II) complex (**403**) and an oxygenated substrate. It is well known that hydroquinones can be oxidized to quinones via a two electron process whereby two Cu(II) ions are reduced to Cu(I) ions[28]. We therefore expect this hydroquinone bridged dinuclear Cu(II) complex **403** to undergo an internal electron transfer process to form a quinone moiety and two Cu(I) ions as in **404**. In the last step we have to reduce the quinone to the hydroquinone by using an external reducing agent, for example by ascorbic acid, or by using electrochemical methods[26]. This completes the catalytic cycle and the hydroquinone-dicopper(I) species **401** can accept the next molecule of $O_2$ to oxidize another substrate molecule. In summary the hydroquinone-quinone moiety acts in this system as an electron shunt between an external reducing agent and the copper ions. This mechanism of electron transfer is reminiscent of the quinone based electron-transfer systems as found for instance in the primary photochemical step in photosynthesis[29] and in synthetic (metallo)porphyrin-quinone electron transfer systems[30].

## 4.2 *Synthesis of a p-hydroquinone containing ligand system*

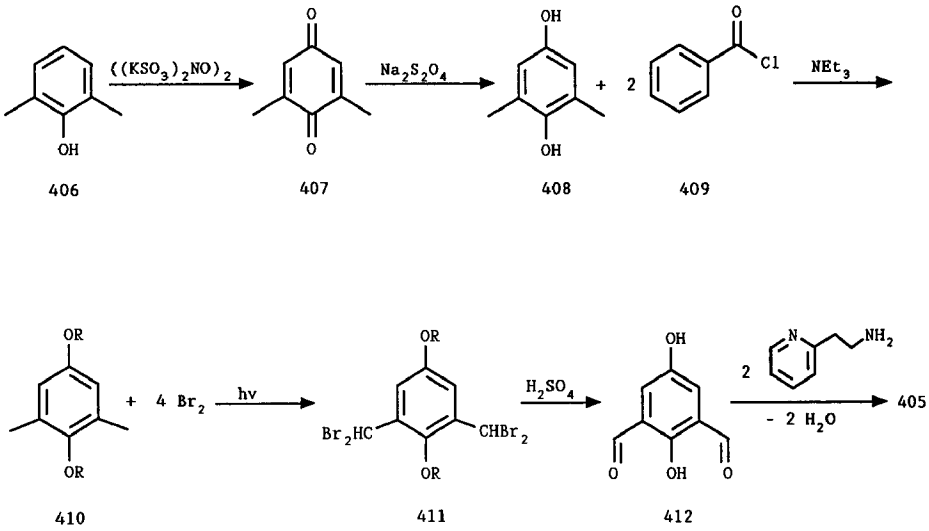
With the purpose of designing dinuclear copper complexes in which a hydroquinone (or quinone) moiety is incorporated, the new ligand 2,6-bis[N-2-(2-pyridyl)ethyl)formimidoyl]-1,4-dihydroxybenzene (**405**) was synthesized (figure 4.1).




405

*Figure 4.1*

The synthesis of ligand **405** is outlined in scheme 4.2. In the first step 2,6-dimethylphenol is oxidized to 2,6-dimethylquinone by a literature procedure using Fremi's salt[31] in a buffered aqueous solution. In this way the yellow quinone **407** could be obtained as a crystalline material in 75% yield. Subsequent reduction of this quinone using sodium dithionite gave 2,6-dimethylhydroquinone (**408**) in 81% yield after crystallization from $H_2O$. In the literature another procedure is described for the synthesis of this compound[32]: an ammonium-persulfate oxidation of 2,6-dimethylphenol (**406**) in basic aqueous solution leads to potassium-4-hydroxy-3,5-dimethylphenylsulfate, which in a subsequent step was hydrolyzed using hydrochloric acid to 2,6-dimethyl hydroquinone (**408**) in 22% overall yield from **406**. But this procedure is laborious and gives low yields of the product. A disadvantage of the present procedure, however, is the limited scale on which the Fremi's salt preparation can be carried out. This salt is highly explosive as we can confirm from personal experience and extreme caution is necessary in handling it[30] (see experimental section)!




*Scheme 4.2*

In the next step protection of the phenolic groups by dibenzoylation using benzoyl chloride (**409**) and triethylamine afforded **410** in 85% yield after crystallization.

Careful radical bromination of **410** with four equivalents of bromine under continuous irradiation gave pure tetrabromo derivative **411** in 83% yield. The formation of **411** can also be achieved using N-bromosuccinimide (yield 79%). Bromination of the aryl groups, a notorious side reaction under certain conditions[33], was not observed and mono- or tribromo-substituted analogues of **411** were not obtained.

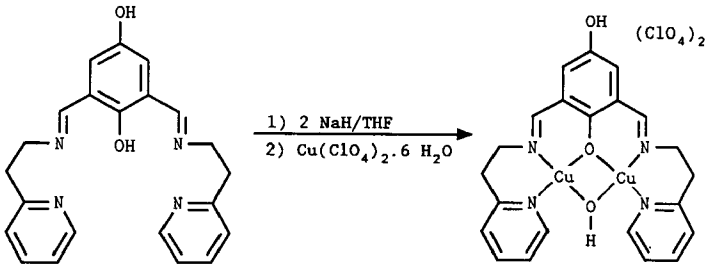
The fact that dibromo-substitution has taken place at each methyl substituent in **411** can also readily be deduced from the singlet observed at 6.60 ppm for the benzylic hydrogen of **411** in the $^1$H NMR spectrum. This high selectivity of dibromo-substitution is probably the result of large steric hindrance of tribromo-substitution due to the large ortho-benzoyl substituent. Exhaustive hydrolysis of **411** in sulphuric acid removes both protective groups and liberates both aldehyde functionalities. Hydroquinone **412** has a simple $^1$H NMR spectrum in $D_2O$/NaOD with singlets at 7.30 and 10.15 ppm for the aryl- and aldehyde- hydrogens respectively. As expected, compound **412** is

rather prone to oxidative decomposition but can be stored well under nitrogen in the cold.

Condensation of **412** with two equivalents of 2-(2-pyridyl)ethylamine in $CH_2Cl_2$ afforded **405** in high yield; sufficiently pure (as determined by $^1H$ NMR) for the preparation of metal complexes.

### 4.3 *Synthesis, electrochemical properties, crystal- and molecular structure of dinuclearcopper(II) complex 413*

In order to prepare dinuclear copper complexes, the ligand **405** was first doubly deprotonated using NaH in tetrahydrofuran to afford the bis-sodium salt. Subsequently it reacted with two equivalents of copper(II)perchlorate hexahydrate in ethanol (scheme 4.3). After recrystallization from aqueous ethanol the dark green dinuclear copper(II) complex **413** was obtained in 36% yield. Elemental analysis gave a C : H : N ratio of 22 : 23.5 : 4. As elemental analysis and spectroscopic data did not provide conclusive evidence for the presence of a quinone or a hydroquinone-copper(II) complex, a molecular structure determination was undertaken.




405 413

*Scheme 4.3*

The crystal structure of **413** was determined by a single crystal X-ray diffraction study. The compound crystallizes in the triclinic space group $P\bar{1}$ with two molecules in the unit cell.

A PLUTO drawing of the molecule, with the adopted numbering scheme and illustrating the puckering, is shown in figure 4.2. Each unit contains one complete molecule of the title compound and two perchlorate residues. Table 4.1 contains selected bond distances and angles respectively (see also experimental section).

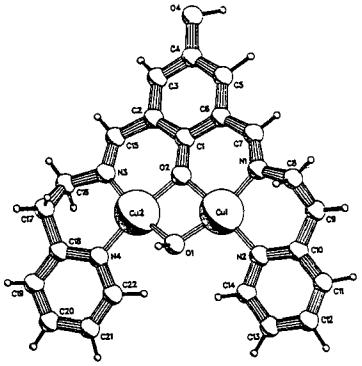


*figure 4.2: Molecular structure with adopted numbering scheme of* ***413*** *(counter ions are omitted for clarity).*

*Table 4.1:* *Selected interatomic distances (Å) and angles (deg) for* ***413.***

| | | | |
|---|---|---|---|
| Cu(1) - Cu(2) | 2.991(2) | O(1) - Cu(1) - O(2) | 78.6(3) |
| Cu(1) - O(1) | 1.922(7) | O(1) - Cu(1) - N(1) | 164.2(3) |
| Cu(1) - O(2) | 1.971(6) | O(1) - Cu(1) - N(2) | 95.8(3) |
| Cu(1) - N(1) | 1.92(1) | O(2) - Cu(1) - N(1) | 91.0(3) |
| Cu(1) - N(2) | 2.014(7) | O(2) - Cu(1) - N(2) | 169.8(3) |
| Cu(2) - O(1) | 1.928(7) | N(1) - Cu(1) - N(2) | 95.9(4) |
| Cu(2) - O(2) | 1.955(7) | O(1) - Cu(2) - N(2) | 78.8(3) |
| Cu(2) - N(3) | 1.939(9) | O(1) - Cu(2) - N(3) | 170.3(3) |
| Cu(2) - N(4) | 2.004(8) | O(1) - Cu(2) - N(4) | 93.2(3) |
| | | O(2) - Cu(2) - N(3) | 91.8(3) |
| | | O(2) - Cu(2) - N(4) | 171.4(3) |
| | | N(3) - Cu(2) - N(4) | 96.3(3) |

The X-ray analysis shows that the molecule is a unique bis copper(II) hydroquinone complex. In contrast to expectation[28], the hydroquinone moiety was not oxidized to a quinone in the presence of the two copper(II) ions in the complex.

Both copper ions are coordinated to a bidentate pyridylethylimine ligand and are bridged by a phenolate and a hydroxy group, adopting a slightly distorted square planar geometry. The molecular structure of **413** shows strong similarities to that of the *p*-deshydroxy analogue **221,** which was obtained by oxygen insertion into the C(1)-aryl hydrogen bond of the corresponding dinuclear Cu(I) complex **216,** derived from ligand **214** (see chapter 2).

The Cu(II)-Cu(II) bond distances of **413** (2.991(2) Å) and **221** (2.990(2) Å)[19] are equal and typical of dinuclear copper complexes containing two, one-atom bridging ligands[34]. The four membered $Cu_2O_2$ unit deviates from planarity with a O(1) - Cu(1) - O(2) - Cu(2) torsion angle of -9.3(3)°. The C(1) - O(2) bond (bond distance 1.32(1) Å) in **413** is shorter than the C(4) - O(4) bond (bond distance 1.38(1) Å), but is slightly longer than the phenolate C - O bond in **221** (bond distance 1.309(7) Å). The C - O bond distances are substantially longer than those in free quinone[35] (1.208 Å), in a Ni(II)-coordinated quinone[36] (1.23 Å), or the average value of 1.27 Å found for the C - O bond length in a semiquinone coordinated to Ni(II)[36]. Combining these data with the results of the refinement using anisotropic thermal parameters, which provided the location of the hydrogen atom at O(4), leads to the conclusion that the phenolic moiety is present as the Cu(II) bridged hydroquinone structure. A semiquinone structure, as has been observed for nickel(II)[37] and copper(II) catecholate complexes[38], is unlikely on the basis of the data provided and the similar Cu - O distances found in **221** and **413** (see tables 2.2 and 4.1).

The findings described stand in contrast to the formation of a quinone-semiquinone adduct of $Ni(II)(ClO_4)_2$ with tetrachlorocatechol[36]. Extensive coordination chemistry of catecholates and semiquinones with group VIII transition metals has been developed[39] since transition metal quinoid adducts provide interesting perspectives as redox catalysts, in biological applications, and in the formation of conducting systems. Although the hydroquinone in **413** is ideally situated for electron transfer to copper ions, this does not readily take place even in the presence of molecular oxygen. It has been suggested for

related nickel complexes[36] that despite the fact that the metal ion acts as an electron sink, back-donation of electrons to a coordinated quinone might take place, depending strongly upon the redox potentials of quinone and metal and the levels of the quinone $\pi$-orbitals and metal d-orbitals.

For example the oxidation potential of acyl-substituted 1,4-hydroquinone is shifted 0.2 V towards a more negative value compared to the corresponding hydroquinone oxidation potential[40]. Hence it is expected that introduction of two electron withdrawing imine substituents makes the oxidation potential even more negative. Electron paramagnetic resonance spectroscopy (EPR) measurements between room temperature and -130°C of dinuclear Cu(II) complex **413** dissolved in dimethyl sulfoxide, showed that complex **413** is EPR silent in this temperature range[41].

Cyclic voltammetric studies with complex **413** under different conditions using dipping methods showed no reversible oxidation-reduction patterns. In acetonitrile as the solvent, only one reduction peak was seen at -0.47 V versus S.C.E. (standard calomel electrode) and a small oxidation peak at -0.12 V versus S.C.E.. In the subsequent runs, the current decreases gradually. Presumably a reduction of the Cu(II) ions to Cu(I) takes place which subsequently decompose into Cu(0) and Cu(II) giving an irreversible decomposition of the complex[42]. A typical example of a cyclic voltammetric measurement of **413** is given in figure 4.3.

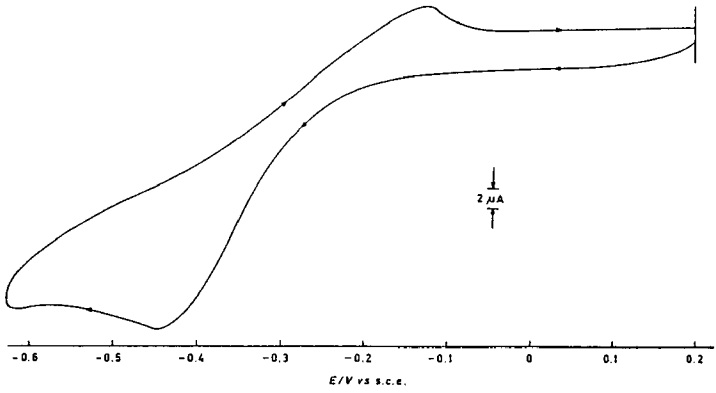
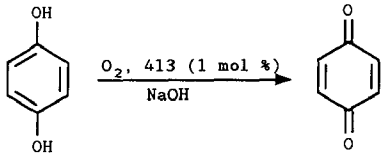



*Figure 4.3: Cyclic voltammogram of complex **413** in acetonitril (30-s dip; SCE and Pt electrodes, 50 mV/s).*

## 4.4 *Catalytic Oxidations*

As was described above, no oxidation of the hydroquinone moiety in **413** takes place using cupric ions and molecular oxygen. Much to our surprise, this dinuclear Cu(II) complex **413** acts as a catalyst for the oxidation of hydroquinone (**414**) to quinone (**415**) using molecular oxygen as the oxidant (scheme 4.4).




414 415

*Scheme 4.4*

Thus in the presence of catalytic amounts (1 mol%) of **413**, hydroquinone **414** is completely converted into **415** under aerobic conditions in 5 min.. Apparently the two electron-withdrawing imine substituents present in ligand **405** sufficiently increase the oxidation potential of the hydroquinone moiety to prevent intramolecular electron transfer to the Cu(II) ions in **413**. However, fast intermolecular electron transfer from **414** to complex **413** can take place.

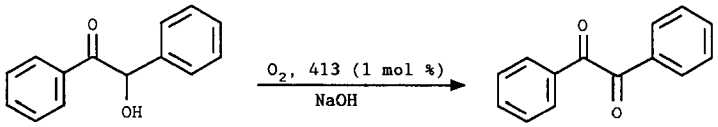
Hydrogen peroxide was not detected as the two electron reduction product from $O_2$ during these oxidations (vide infra). Furthermore, we have not obtained any indication for the involvement of the hydroquinone moiety in **413** during the catalytic oxidation, other than acting as a bridging ligand between the two Cu(II) ions.

Thus **405** was recovered unchanged after the oxidation as shown by $^1$H NMR after liberation of the ligand using Karlin's method[43]. This is in accordance with the observed stability of **413** under aerobic conditions.

Since oxidation of the hydroquinone to quinone moiety in **413** does not take place to form the corresponding bis Cu(I) complex **404** (scheme 4.1), the activation of $O_2$ is prohibited and complex **413** is not active as a catalyst for oxygenation reactions. To obtain further evidence for the ability of **413** to act

as a dehydrogenation catalyst, the conversion of $\alpha$-hydroxyketones was examined.

In a typical example benzoin (**416**) is converted into benzil (**417**) (scheme 4.5). A rapid dehydrogenation takes place under basic conditions and a turnover of 1032/hour (based on catalyst) was reached. As base is essential for this oxidation reaction to occur, it proved to be possible to control the oxidation of **416** by the rate of addition of base. The results show a stoichiometric reaction with respect to NaOH, $O_2$ and benzoin.



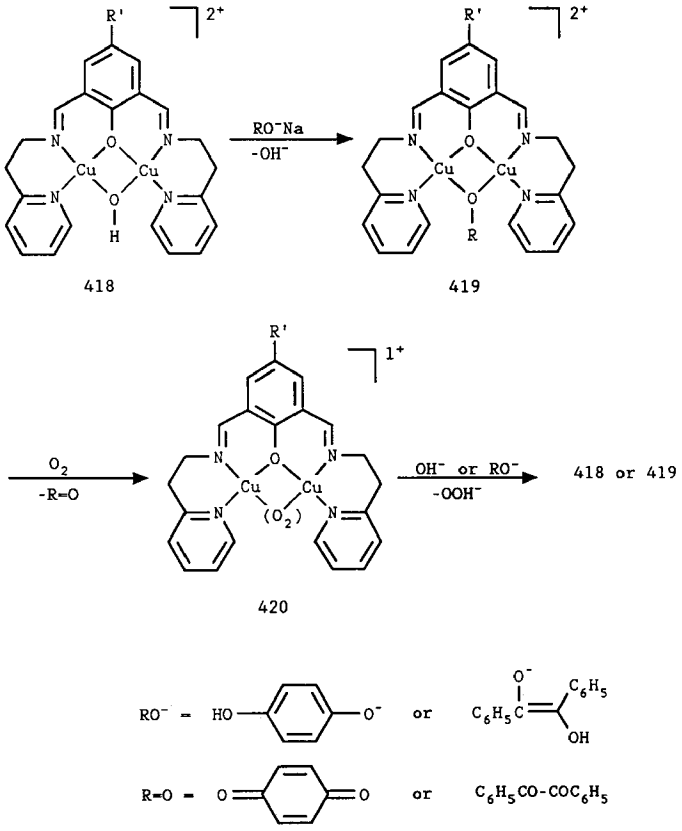

416 417

*Scheme 4.5*

A mechanistic rational for the catalytic dehydrogenation mediated by **413**, in accordance with the data obtained, is given in scheme 4.6. Extensive mechanistic studies will be necessary to substantiate this scheme.

Binding of the substrate to one or two copper ions as in **419** is followed by a two-electron transfer to yield a dinuclear Cu(I) complex. Subsequent binding of molecular oxygen is thought to result in the formation of peroxy complex **420**. Similar binding of phenolate anions followed by $O_2$ binding to dinuclear Cu(II) complexes has been proposed as the first step in the catalytic oxidative polymerization of 2,6-dimethylphenol[44]. Substantial evidence for the formation of peroxo dicopper(II) complexes from phenoxo-bridged dicopper(I) complexes has been reported by Karlin and co-workers[45]. Furthermore, a recent crystal structure of a 1,2-peroxo dicopper(II) complex without a bridging ligand between the two copper centers has been reported[46].

As the addition of base is essential for the oxidation to occur, we speculate that the role of the base is to deprotonate the substrate (ROH) either prior to or after binding to one or two copper ions in the dinuclear complex. This is in line with mechanistic proposals in oxidative phenol




*Scheme 4.6*

coupling[44]. Alternative mechanisms to the one shown in scheme 4.6 might be proposed; for instance the redox reaction of complex **420** with deprotonated substrate is an attractive possibility. This points to a reversal of the sequence as shown in scheme 4.6. It should be emphasized that one mole of $O_2$ per mole of substrate is consumed indicating a two electron transfer process contrary to four electron transfer processes that lead ultimately to $H_2O$ as was observed in copper (II)-mediated oxidative phenol coupling[44]. In situ (catalytic) decomposition of the hydroperoxide anion cannot be excluded. In a control experiment 30% $H_2O_2$ was added to a methanolic solution of **418** and NaOH. We were not able to detect peroxide after 1 h. at room temperature which indicates $H_2O_2$ decomposition.

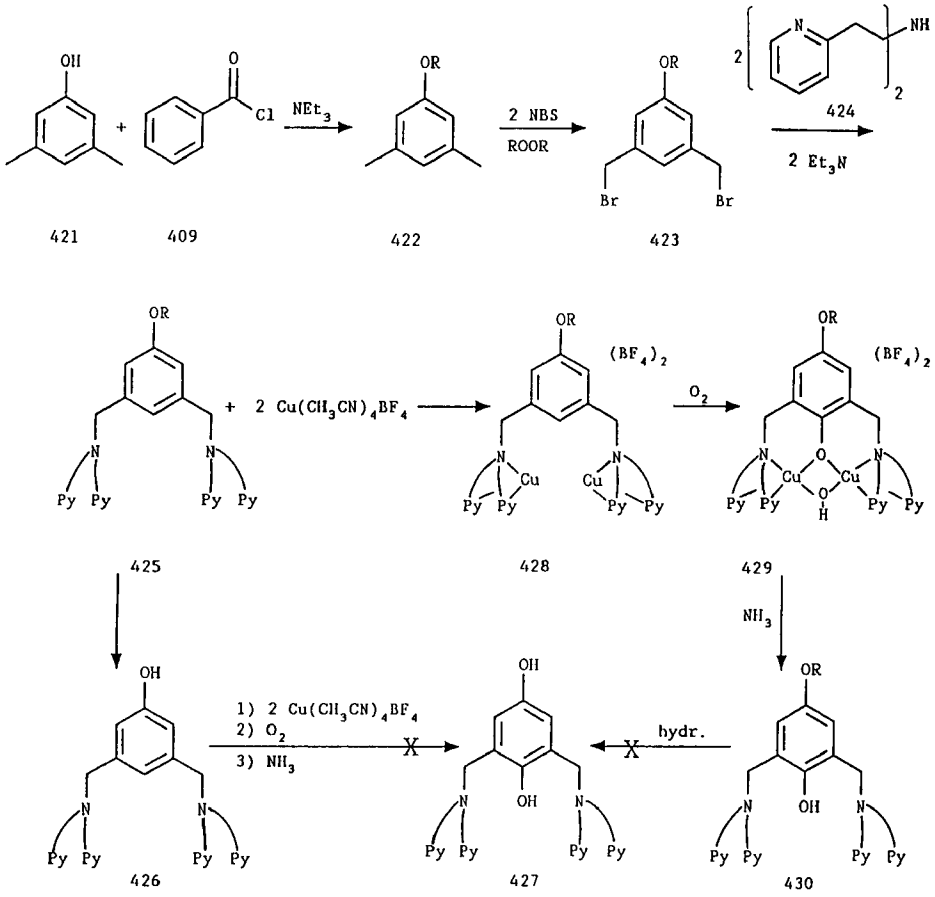
With respect to substrate oxygenation it is relevant that a hydroperoxo copper complex (Cu-OOH species) has been proposed as an essential intermediate in certain copper monooxygenases[48]. Furthermore active oxidizing agents based on metalloporphyrins are obtained from M-OOR intermediates[49]. Karlin and co-workers[46] found evidence for electrophilic activation (i.e. protonation) during oxygen transfer in peroxo dicopper(II) complexes. In line with these observations it is reasonable to assume that under the basic conditions applied in the oxidation reactions described here, no hydroperoxo dicopper(II) complex is formed and consequently no oxygenation can take place.

### 4.5 *Attempted synthesis of an alternative p-hydroquinone dinuclear copper(II) catalyst*

The presence of a hydroquinone or phenol moiety in the afore-mentioned ligands is only essential for bridging the Cu(II) ions but has, as far as was observed experimentally, no role in the redox process. Furthermore, it can be concluded that the intended application of the hydroquinone moiety as an electron shunt between an external reducing agent and the Cu(II) ions (and thus molecular oxygen) is not possible with the present model system. Therefore we decided to prepare another hydroquinone containing ligand system in which the imine double bonds are not present making the hydroquinone oxidation more favourable. A modification of the dinucleating ligand system described by Karlin and co-workers[43] (see section 2.3) was used together with the dicopper(I) dioxygen induced hydroxylation reaction (chapter 2) to incorporate one of the oxygen atoms (in the 1-position) of the hydroquinone moiety into the ligand. The synthesis of this ligand system is outlined in scheme 4.7.

In the first step 3,5-dimethylphenol (**421**) was protected with benzoyl chloride (**409**) to give the corresponding ester in 90% yield after distillation. When ester **422** was allowed to react with two equivalents of

N-bromosuccinimide using benzoyl peroxide as radical initiator, an almost statistical mixture of mono-, di- and tri-brominated products was obtained. From this mixture the $\alpha,\alpha'$-dibromomethylphenol-ester **423** could be isolated by crystallization from MeOH as white needles in 32% yield. According to $^1$H NMR and combustion analysis this was pure dibrominated product **423.**



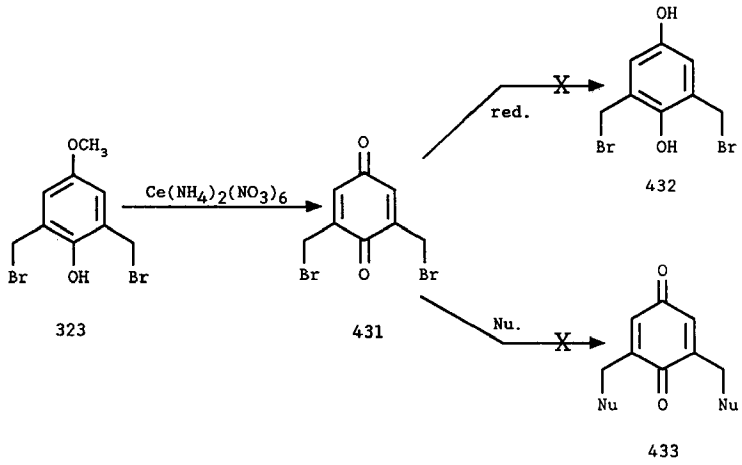

*Scheme 4.7 (Py = 2-pyridyl, R = PhCO)*

In the next step **423** was allowed to react with two equivalents of bis(2-(2-pyridyl)ethyl)amine (**424**) and two equivalents of triethylamine, to give, after chromatographic purification on $SiO_2$, the hexadentate ligand **425** in 65% yield (pure according to $^1$H NMR) as a colourless oil. This ester **425** could be hydrolyzed using NaOH in methanolic solution to provide phenol **426** in about

50% yield as a yellow oil. This oil was sufficiently pure for further use, according to $^{1}H$ NMR, $^{13}C$ NMR and HRMS. On reaction of **426** with two equivalents of $Cu(CH_3CN)_4BF_4$ a brown poorly soluble powder was isolated. This product could not be oxidized (oxidation at the 1-position of the aromatic nucleus was desired) using molecular oxygen because of its poor solubility in all kinds of solvents. Upon long standing in $CH_3CN/CH_2Cl_2$ mixtures, a green coloured solution appeared probably due to "simple" Cu(I) oxidation because, when the ligand was isolated by an ammonia extraction procedure, no oxidation at C-1 was found ($^{1}H$ and $^{13}C$ NMR). Therefore it was decided to leave the hydroxyl group protected during the copper complexation reaction and subsequent oxidation. Reaction of **425** with two equivalents of $Cu(CH_3CN)_4BF_4$ gave a yellow precipitate which was not further characterized. Presumably dinuclear Cu(I) complex **428** is formed in confirmity with the work described by Karlin and co-workers for the 5-hydrogen *m*-xylyl analog **202** of **425** (see section 2.3). Upon atmospheric oxidation of this complex, performed in a $CH_2Cl_2/CH_3CN$ (10 : 1) solvent mixture, a rapid colour change from yellow to dark green was observed. In accordance with the oxidation of **202** (see section 2.3) it is presumed that oxidation of **428** yields the phenoxy-hydroxy bridged dinuclear Cu(II) complex **429**, which was not isolated. After six hours of oxidation the ligand was liberated from the Cu(II) salts by using an ammonia extraction procedure, giving exclusively the hydroxylated product **430** in 85% yield, starting from **425**. The incorporation of oxygen into ligand **425** was easily proved by $^{13}C$ NMR APT techniques. In the $^{13}C$ APT spectrum of **430** the xylyl bridge carbon atom at 125.7 ppm had completely inverted compared to the $^{13}C$ ATP spectrum of **425**. This means that no proton is attached to the C-1 atom in **430**. It is noteworthy that **429** is obviously a stable complex that does not react further to a quinone-bridged dinuclear copper(I) complex[50b]. Other examples are known in which metal ions (e.g. Ce(IV)) are able to oxidize mono-protected hydroquinones to quinones (vide infra).

In the last step of the synthesis of ligand **427** the ester protecting group had to be removed. This deprotection, however, could not be

accomplished by any method thus far tried. Upon basic hydrolysis, using various bases, only starting ligand or bis(2-(2-pyridyl)ethyl)amine (**424**) could be isolated as the product. Upon acidic hydrolysis, using several conditions, no cleavage of the ester was found. Reduction of the ester by $LiAlH_4$ gave no pure product. Therefore we had to stop at this stage of the synthesis. Other attempts to prepare the desired compound by way of a 2,6-dibromomethyl quinone (**431**) intermediate, obtained from **323** by a cerium ammonium nitrate oxidation[50], failed because of the lability of the bromomethyl groups towards reduction in the subsequent step and the reactivity of the quinone towards nucleophilic attack (scheme 4.8).




*Scheme 4.8*

In conclusion we have reported here the synthesis of a new ligand system **405** containing a hydroquinone moiety capable of forming dinuclear complexes. The molecular structure of a previously unknown, stable, dinuclear hydroquinone Copper(II) complex **413** was determined[54].

Furthermore, efficient catalytic dehydrogenations of hydroquinone and $\alpha$-hydroxyketones (e.g. hydroxy acetone, benzoin) using $O_2$ were found. However, we were not able to prepare a suitable ligand in which the two copper ions are coordinated to a hydroquinone moiety without electron withdrawing substituents. Therefore we could not accomplish electron transfer

from a hydroquinone bridged ligand to two Cu(II) ions to form a dinuclear copper(I) complex. As a consequence no dioxygen could be activated for oxygenation (O-Transfer) of external substrates. To achieve this goal several alternatives for the preparation of ligand **427** can be thought of: e.g. careful reduction of the ester moiety in **430** or protection of the phenolic ligand by $SiR_3$ protecting groups which can be removed more easily.

Finally the Cu(I) promoted hydroxylation reaction, as described in scheme 4.7 is an example of the utility of this methodology in synthesis for the preparation of phenols and mono-protected hydroquinones that are otherwise difficult to obtain.

## 4.6 *Experimental Part* (see also chapter 2)

All experiments with hydroquinones were performed under an inert ($N_2$) atmosphere. For the oxidation experiments, pure oxygen (Air products) was used. Oxygen uptake was measured using manometric techniques. Tetrahydrofuran was distilled from sodium benzophenone ketyl under a $N_2$ atmosphere. All other solvents were distilled before use. 2,6-Xylenol (Janssen) was used as such.

EPR measurements were performed by Klaas Hovius on a Varian E4 spectrometer. Cyclic Voltommetry was carried out by Hans Roedelof wit a Parc-174 polarograph directed by a 175 Programmer (Parc) or by a Parc 273 potentiostat. The solutions were freshly prepared in $CH_3CN$ (Aldrich P.A. quality) with 0.1 M $Bu_4NClO_4$ as the electrolyte.

**2,6-Dimethyl-1,4-hydroquinone (408)**

To a solution of 60 g of $KH_2PO_4$ in 700 ml $H_2O$ was added 10 g (82 mmol) of 2,6-xylenol (**406**) dissolved in 200 ml of methanol. Freshly prepared Fremi's salt[30] (caution explosive !) (60 g, 112 mmol) was subsequently added in two portions to the well-stirred mixture prepared above.

Stirring was continued for 1 h. at room temperature and the resulting reaction mixture was extracted with diethyl ether (3 x 50 ml). The organic extracts were dried over $MgSO_4$, the solvent removed in vacuo and the solid residue purified by crystallization from petroleum ether (60-80) to give 8.0 g (75%) of yellow crystalline **407**. m.p. 74-75°C (lit.[50] 73-75°C).

A solution of 5.0 g (37 mmol) of 2,6-dimethylquinone (**407**) in $CHCl_3$ (100 ml) was vigorously shaken for 10 minutes with a solution of $Na_2S_2O_4$ (10 g) in aqueous NaOH (8.0 g

NaOH in 100 ml $H_2O$). The aqueous layer was separated, acidified (aq. HCl) and extracted with $CHCl_3$ (2 x 50 ml). The combined chloroform solutions were dried over $MgSO_4$ and the solvent removed by rotatory evaporation to yield a white solid. Crystallization from $H_2O$ gave 4.1 g (81%) of **408**. m.p. 149-151°C (lit.[51] 151-152°C).

**1,4-Benzoyloxy-2,6-dimethylbenzene (410)**

To a solution of 4.0 g (29 mmol) 2,6-dimethylhydroquinone (**408**) and 5.9 g (58 mmol) triethylamine in 200 ml of $CH_2Cl_2$ was added, at room temperature over a period of one hour, 8.2 g (58 mmol) of benzoylchloride (**409**). The resulting mixture was stirred for an additional hour and subsequently poured into 100 ml of $H_2O$. The $CH_2Cl_2$ layer was separated, washed with 2 N aqueous HCl (twice), aqueous 10% NaOH solution and brine. After drying over $MgSO_4$ and removal of the solvent by rotary evaporation, the solid residue was crystallized from petroleum ether (60-80). There was obtained 8.3 g (85%) of pure **410** as white needles. m.p. 117.5-118.4°C; $^1$H NMR ($CDCl_3$): $\delta$ 2.23 (s, 6H), 6.97 (s, 2H), 7.37-7.73 (m, 6H), 8.08-8.37 (m, 4H); $^{13}$C NMR ($CDCl_3$): $\delta$ 16.44, 121.34, 128.42, 128.53, 128.99, 129.43, 130.03, 131.64, 133.41, 133.54, 145.77, 148.02, 164.11, 165.05. Analysis calculated for $C_{22}H_{18}O_4$: C: 76.42, H: 5.32, found: C: 76.30, H: 5.32. HRMS calculated for $C_{22}H_{18}O_4$: 346.120, found 346.119.

**1,4-Benzoyloxy-2,6-bis(dibromomethyl)benzene (411)**

To a stirred solution of 7.0 g (20.2 mmol) of **410** in 150 ml $CCl_4$, heated at reflux and continuously irradiated with an IR photolamp, was slowly added over a one hour period, 13.0 g (81 mmol) of bromine. After the addition was completed, the resulting mixture was heated and irradiated for an additional period of 12 h.. By that time the bromine had completely disappeared. The solvent was removed by distillation and the residue purified by crystallization from petroleum ether (60/80) affording **411** as white crystalline material; yield 11.2 g (83%). m.p. 177.5-179.7°C; $^1$H NMR ($CDCl_3$): $\delta$ 6.57 (s, 2H), 7.33-7.76 (m, 6H), 7.83 (s, 2H), 8.03-8.36 (m, 4H); $^{13}$C NMR ($CDCl_3$): $\delta$ 32.17, 125.20, 127.40, 128.70, 129.07, 130.28, 130.44, 130.75, 134.04, 134.77, 135.87, 137.33, 149.25, 163.55, 164.22. HRMS calculated for $C_{22}H_{14}Br_4O_4$: 657.761, found: 657.763. Analysis calculated for $C_{22}H_{14}Br_4O_4$: C: 39.88, H: 2.11, Br: 48.34, found: C: 39.55, H: 2.11, Br: 48.70.

**1,4-Hydroquinone-2,6-dicarboxaldehyde (412)**

A solution of 5.0 g (7.3 mmol) of **411** in 50 ml of concentrated $H_2SO_4$ was stirred at room temperature for 16 h.. The solution was slowly poured onto 150 g of crushed ice and the aqueous mixture was subsequently extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with aqueous $NaHCO_3$ (3 x 30 ml of a 1 N solution), dried over

$MgSO_4$ and the solvent removed in vacuo. Crystallization of the yellow residue from $H_2O$ gave the title compound **412**; yellow solid, 0.45 g (40%). m.p. 170-174°C; $^1$H NMR (NaOD,$D_2O$): $\delta$ 7.30 (s, 2H), 10.15 (s, 2H); $^{13}$C NMR ($D_2O$,NaOD,$CD_3OD$): $\delta$ 118.86, 120.05, 145.29, 163.17, 185.42. HRMS calculated for $C_8H_6O_4$: 166.027, found: 166.028.

**2,6-Bis[N-(2-(2-pyridyl)ethyl)formimidoyl)]-1,4-dihydroxybenzene (405)**

To a stirred solution of 0.10 g (0.6 mmol) **412** in 50 ml $CH_2Cl_2$ was added 0.147 g (1.2 mmol) of 2-(2-pyridyl)ethylamine. The mixture was stirred at room temperature for 1 h. and subsequently 1.0 g of $Na_2SO_4$ was added. After being stirred for an additional hour, the solution was filtered and evaporated to dryness to afford **405** as a red-brown oil; yield 0.21 g (93%), which was homogeneous by $^1$H NMR. $^1$H NMR ($CDCl_3$): $\delta$ 3.15 (t, 4H), 3.95 (t, 4H), 7.0-7.3 (m, 6H), 8.40 (s, 2H), 8.55 (d, 2H), 9.82 (s, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 38.99, 59.16, 119.71, 121.11, 121.44, 123.62, 136.49, 148.65, 148.86, 155.64, 158.92, 161,62. HRMS calculated for $C_{22}H_{22}N_4O_2$: 374.174, found: 374.173.

**$\mu$-Hydroxy-$\mu$-[2,6-bis[N-(2-(2-pyridyl)ethyl)formimidoyl]-4-hydroxyphenolato]dicopper(II) tetrafluoroborate $Cu_2$(2,6-BPB-1-O-4-OH)$(BF_4)_2$ (413)**

Sodium hydride (0.027 g, 1.13 mmol) was suspended in THF (30 ml) and treated with 0.21 g (0.56 mmol) **405** dissolved in THF (10 ml). The resulting solution was stirred and heated at reflux for 1 h.. The solvent was removed in vacuo and the yellow disodium salt was dissolved in absolute ethanol (20 ml) and added to a solution of 0.42 g (1.13 mmol) $Cu(ClO_4)_2.6H_2O$ in absolute ethanol (10 ml). The resulting mixture was heated at reflux for two hours and subsequently concentrated in vacuo. The solid residue was crystallized from MeOH/$H_2O$ to afford dark green crystalline **413**; yield 0.143 g (36%). Analysis calculated for $C_{22}H_{22}Cl_2Cu_2N_4O_{11}$: C: 36.87, H: 3.07, N: 7.82, found: C: 36.79, H: 3.28, N: 7.77. IR (KBr): 3500 (br.OH), 1650, 1615, 1580, 1100 (CBr str.), 850, 780 cm$^{-1}$.

**Crystal structure determination of 413**

The single crystal X-ray determination was performed at room temperature with MoK$\alpha$ radiation ($\lambda$ = 0.71073 Å) on an Enraf-Nonius CAD-4F diffractometer equipped with a graphite monochromator using the $\omega$-2$\Theta$ scan technique. A suitable green coloured plate shaped crystal of dimension 0.15 x 0.14 x 0.07, cleaved from an intergrow specimen, was obtained by crystallization from MeOH/$H_2O$ and crystallized in the triclinic space group $P\bar{1}$ with a = 9.399(2), b = 10.469(1), c = 14.612(4) Å, $\alpha$ = 102.72(2), $\beta$ = 100.71(2), $\gamma$ = 104.60(2)° and V = 1312.1(5) Å$^3$. For Z = 2 the calculated density is 1.813 gcm$^{-3}$. For 1.48 < $\Theta$ < 22.0 3198 reflections were obtained, 2101 reflections with I $\geq$ 2.5 $\sigma$(I) were only used in the refinements.

The structure was solved by Patterson methods and subsequent partial structure expansion (SHELXS86[53]) completed by Fourier techniques. Refinement using anisotropic thermal parameters followed by difference Fourier synthesis resulted in the location of 18 hydrogen atoms; the remaining four hydrogen atoms (H(14), H(82), H(92) and H(172)) were introduced at calculated positions (C - H = 1.0 Å). Thereby the H atoms found served to determine the conformation. Due to the low observation to parameter ratio in the final calculation, hydrogen atoms were refined in the riding mode and with one common temperature factor. Refinement on F by block-diagonal least-squares techniques with anisotropic thermal parameters for the non-hydrogen atoms and one overall isotropic temperature factor for the hydrogen atoms converged at $R_F$ = 0.050 (wR = 0.050). High thermal motion, but no resolvable disorder, was sited for the C(8) atom. A final difference Fourier map did not show unusual features.

**Catalytic Oxidations with 413** Typical procedure: oxidation of benzoin.

Benzoin (**416**) (0.183 g, 0.86 mmol) and **413** (0.007 g, 0.01 mmol) were dissolved in 10 ml of methanol in a 100 ml three-necked bottle. The reaction vessel was put in a thermostated bath maintained at 19°C and connected to a gas buret filled with dioxygen. The mixture was equilibrated for 30 minutes. Subsequently 0.040 g (1.0 mmol) of NaOH dissolved in 1 ml methanol was added at once. The reaction mixture was vigorously shaken and the oxygen uptake measured.

After 2 min. oxygen uptake declined; and after 5 min., it stopped completely, resulting in a total $O_2$ consumption of 20.5 ± 1 ml (0.85 ± 0.05 mmol). The methanolic solution was acidified with aqueous HCl, and most of the MeOH was evaporated. The resulting aqueous layer was extracted three times with 10 ml of diethyl ether.

The combined ether layers were dried over $MgSO_4$ and evaporated to dryness. The white solid was crystallized from petroleum ether (40/60). Benzil (**417**) (0.178 g, 98%), identical in all respects with an independent sample, was obtained. Traces of benzaldehyde (approx. 1%) were found. If 0.009 g (0.23 mmol) NaOH was used instead of stoichiometric amounts of base the oxygen uptake stopped after 5.8 (± 0.5) ml (0.24 ± 0.03 mmol) $O_2$ had been consumed.

The oxidation of hydroquinone (**414**) was performed following the typical procedure described above. The product was identical in all respects with an independently prepared sample; however, only small amounts of product could be isolated because of the instability of the quinone under the specific reaction conditions.

**Benzoyloxy-3,5-dimethylbenzene (422)**

To a solution of 12.2 g (0.1 mol) 3,5-dimethylphenol (**421**) and 11.0 g (0.11 mol) triethylamine in 150 ml $CH_2Cl_2$ was slowly added 14.1 g (0.1 mol) benzoyl chloride (**409**) at

such a rate that the solution was gently refluxing. After all the acid chloride was added stirring was continued for 2 h.. Next 100 ml $H_2O$ was added and the layers were separated. The $CH_2Cl_2$ layer was washed successively with 1 N HCl (2 x 50 ml), 1 N NaOH (2 x 50 ml), 1 N HCl (1 x 25 ml) and 1 N $NaHCO_3$ (1 x 50 ml). After drying on $MgSO_4$ the filtrate was evaporated to dryness to give a residue which was distilled at 150°C (0.01 mm Hg) to provide 19.3 g (90%) **422** as a colourless oil. $^1$H NMR ($CDCl_3$): $\delta$ 2.27 (s, 6H), 6.78 (s, 3H), 7.28-7.58 (m, 3H), 8.05-8.28 (dd, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 20.95, 119.02, 127.31, 128.23, 129.48, 129.82, 133.16, 138.97, 150.64, 165.00 ppm.

**Benzoyloxy-3,5-$\alpha$,$\alpha$'-dibromomethylbenzene (423)**

A solution of 10 g (44 mmol) **422**, 16 g (90 mmol) N-bromosuccinimide and 100 mg benzoyl peroxide in 100 ml $CCl_4$ was heated under reflux for 2.5 h.. After cooling to room temperature, the succinimide was removed by filtration and the $CCl_4$ layer evaporated to dryness to give a semi solid residue. This material was crystallized from dry methanol. In this way 5.4g (32%) of white crystalline **423** was obtained. m.p. 130.1-132.9°C; $^1$H NMR ($CDCl_3$): $\delta$ 4.77 (s, 4H), 7.13-7.67 (m, 4H), 7.20 (s, 2H), 8.05-8.28 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 31.86, 122.26, 126.78, 128.52, 128.92, 130.02, 133.70, 139.65, 150.98, 164.64 ppm. HRMS calculated for $C_{15}H_{12}O_2Br_2$: 381.921, found: 381.921. Analysis calculated for $C_{15}H_{12}O_2Br_2$: C: 46.90, H: 3.13, Br: 41.69, found: C: 47.15, H: 3.19, Br: 41.36.

**Bis(2-(2-pyridyl)ethyl)amine (424)**

This compound was prepared according to a literature procedure described in ref. 52. Starting from 10.5 g 2-vinylpyridine and 12.2 g 2-(2-pyridyl)ethylamine (**213**), 9.1 g (46%) of **424** was obtained as a colourless oil after distillation (170°C, 0.01 mm Hg). $^1$H NMR ($CDCl_3$): $\delta$ 1.60 (br s, 1H), 2.95 (br, 8H), 6.80-7.13 (m, 4H), 7.30-7.73 (m, 2H), 8.43 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 37.85, 48.62, 120.48, 122.57, 135.57, 148.61, 159.64 ppm. HRMS calculated for $C_{14}H_{17}N_3$: 227.142, found: 227,142.

**3,5-$\alpha$,$\alpha$'-Di[bis(2-(2-pyridyl)ethyl)amine]methyl-1-benzoyloxybenzene (425)**

To a solution of 384 mg (1 mmol) **423** and 202 mg (2 mmol) triethylamine in 25 ml ethylacetate was added 454 mg (2 mmol) of **424**. This mixture was stirred for 16 h. after which period the white precipitate was removed by filtration. The filtrate was evaporated to dryness to give crude **425** as an oil which was chromatographed on silicagel with methanol as eluent ($R_f$ = 0.65 for **425**). A total yield of 410 mg (61%) of a pure product (**425**) was obtained.
$^1$H NMR ($CDCl_3$): $\delta$ 2.91 (br s, 16H), 3.64 (s, 4H), 6.91-7.03 (m, 9H), 7.39-7.55 (m, 6H), 7.61 (t, 1H), 8.16 (d, 2H), 8.42 (br s, 4H); $^{13}$C NMR ($CDCl_3$): $\delta$ 35.69, 53.52, 57.89, 119.78, 120.67, 123.14, 125.70, 128.24, 128.55, 129.73, 133.15, 135.78, 140.90, 148.72, 150.58, 160.19, 164.62. No

mass analysis could be obtained from this compound due to its instability under the EI conditions. Even chemical ionization techniques using $NH_3$, did not give ($M^+$ + 1) peaks.

**2,6-α,α'-Di[bis(2-(2-pyridyl)ethyl)amine]methyl-1-hydroxy-4-benzoyloxybenzene (430)**

To a suspension of 344 mg (1.1 mmol) $Cu(CH_3CN)_4BF_4$ in 10 ml THF in a double Schlenk apparatus, under $N_2$ atmosphere, was added 328 mg (0.5 mmol) of **430** in 10 ml THF. After stirring for 16 h., a yellow precipitate was formed which was removed from the supernatant THF by filtration. The yellow precipitate was dissolved in 30 ml $CH_2Cl_2/CH_3CN$ (20 : 1) and the resulting orange solution was exposed to the open atmosphere. Immediately a colour change from orange to dark green was observed. Next, this solution was stirred for an additional 6 h., after which 10 ml concentrated aqueous ammonia was added. The $CH_2Cl_2$ layer was separated and extracted once more with ammonia (10 ml). After drying over $Na_2SO_4$ and filtration, the $CH_2Cl_2$ was evaporated to yield 290 mg (85%) of **430** as a yellow oil which was sufficiently pure according to $^1H$ and $^{13}C$ NMR. $^1H$ NMR ($CDCl_3$): δ 2.98 (m, 16H), 3.76 (br s, 4H), 6.75 (s, 2H), 6.99 (m, 8H), 7.46 (m, 6H), 7.59 (t, 1H), 8.15 (d, 2H), 8.42 (br s, 4H); $^{13}C$ NMR ($CDCl_3$): δ 35.05, 53.32, 54.35, 120.59, 120.89, 123.18, 124.03, 128.22, 129.59, 129.71, 133.10, 136.09, 142.38, 148.79, 153.21, 159.59, 165.15 ppm. No mass analysis could be obtained from this compound due to its instability under EI and CI conditions.

**3,5-α,α'-Di[bis(2-(2-pyridyl)ethyl)amine]methylphenol (426)**

A solution of 420 mg (0.62 mmol) **425** and 200 mg (5 mmol) NaOH in 20 ml MeOH was heated under reflux for 1 h.. After evaporation of the solvent, the residual oil was dissolved in 10 ml $H_2O$ and acidified using 1 N HCl to a pH of approximately 8 - 9. This water layer was extracted three times with 25 ml $CH_2Cl_2$. The $CH_2Cl_2$ layers were collected, dried over $Na_2SO_4$ and filtered. Evaporation of the $CH_2Cl_2$ in vacuo yielded 270 mg (75%) of **426** as a yellow oil, sufficiently pure for further use according to $^1H$ and $^{13}C$ NMR. $^1H$ NMR ($CDCl_3$): δ 2.88 (br s, 16H), 3.53 (br s, 4H), 6.57 (br s, 3H), 6.78-7.17 (m, 8H), 7.23-7.60 (m, 4H), 8.30-8.50 (m, 4H), 8.87 (br s, 1H); $^{13}C$ NMR ($CDCl_3$): δ 35.18, 53.31, 57.95, 114.36, 114.41, 120.77, 123.14, 136.06, 140.22, 148.33, 157.07, 160.10 ppm. Mass calculated for $C_{36}H_{40}N_6O$: 572, found: 572 (UV detection).

**2,6-α,α'-Dibromomethyl-1,4-quinone (431)**

To a solution of 310 mg (1 mmol) **323** in 10 ml acetonitrile was added 1.6 g (3 mmol) $Ce(NH_4)_2(NO_3)_6$ in 15 ml $H_2O$. After 1 h. of stirring 50 ml $CH_2Cl_2$ was added and stirring continued for 5 min.. After the $CH_2Cl_2$ layer was separated the aqueous water layer was extracted once more with 25 ml $CH_2Cl_2$. The combined organic layers were dried over $MgSO_4$ and, after filtration, evaporated to dryness to give 300 mg (98%) of a yellow oil which was pure **431** according to $^1H$ NMR. $^1H$ NMR ($CDCl_3$): δ 4.21 (s, 4H), 6.83 (s, 2H) ppm.

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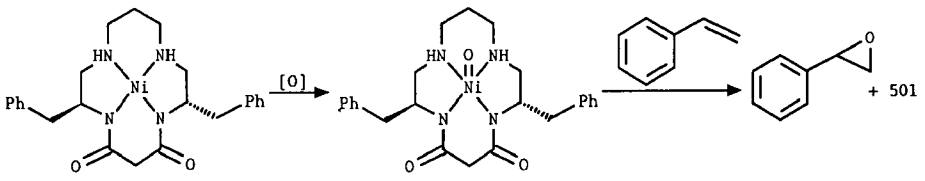
# CHAPTER 5

## SYNTHESIS, STRUCTURE AND CATALYTIC ACTIVITY OF NEW CHIRAL DINUCLEAR COPPER(II) AND NICKEL(II) COMPLEXES

### 5.1 *Introduction*

In the previous chapters we described stoichiometric hydroxylations and catalytic dehydrogenations using dinuclear copper(I) and copper(II) complexes and dioxygen as the terminal oxidizing agent. Our principal goal, however, was the catalytic introduction of oxygen atoms into substrate molecules to mimic the action of mono- and/or dioxygenases. As we did not achieve this goal by using copper complexes, we decided to turn our attention to other metal complexes. During our investigations on dinuclear copper complexes as well as other dinuclear metal complexes, mononuclear nickel complexes derived from tetra aza-macrocycles and Schiff bases were reported by two groups to be able to catalyze the epoxidation of alkenes using iodosylbenzene or sodium hypochlorite as the oxygen donors[1,2]. In these reactions it is proposed that a nickel-oxo species participates as an oxygen transfer agent in a "shunt" or "rebound" mechanism[3] (scheme 5.1).




501 502

*Scheme 5.1 ([O] = Ph-IO, NaOCl)*

Although the structures of the active oxidants are still unknown, three active intermediates have been postulated[2] (figure 5.1).

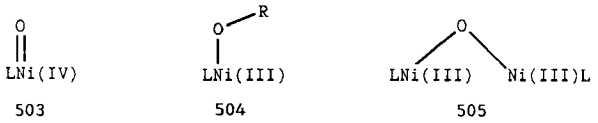
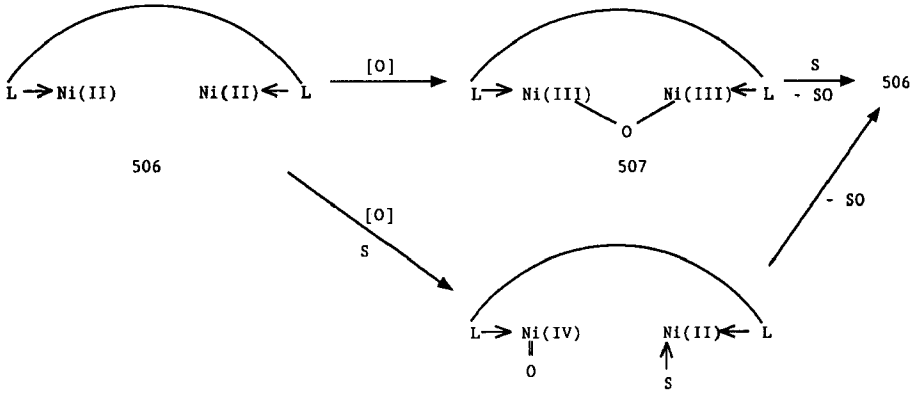



*Figure 5.1 (L = ligand)*

Species **503**, a nickel(IV)-oxo complex, can be formed from iodosylbenzene and LNi(II) by a process analogous to that previously established for related cationic chromium complexes. The structure of a similar chromium-oxo complex has been determined[4]. The reactivity patterns and effects of donor ligands with the proposed Ni(IV)-oxo species are strongly reminiscent of the behavior previously observed for well defined manganese(III) catalysts under similar conditions[5]. Structure **504**, a nickel-oxidant complex, is also a potential intermediate although little evidence is available to support it[5b,6]. A $\mu$-oxo dimer **505** could readily be formed from a reaction between LNi(IV)O (**503**) and LNi(II) which is akin to the observed behavior of manganese porphyrins during epoxidation[2,5]. In contrast with the $\mu$-oxo-manganese dimer, which is inactive as olefin oxidant, **505** could be capable of oxygen transfer to a substrate strongly depending upon the ligands present.

Considering these possible intermediates, we decided to synthesize and investigate the activity of bis nickel(II) complexes towards epoxidation of olefines. In these complexes the nickel nuclei lie next to each other in such a manner that they are well suited to form a $\mu$-oxo-Ni(III) dimer (species **507**) intermediate (scheme 5.2). On the other hand, if this does not happen but instead complex **508** is formed, the second nickel(II) nucleus might activate the alkene substrate by coordination[8], thereby bringing the metal- oxo species and substrate in close proximity and making the oxo transfer more favourable.

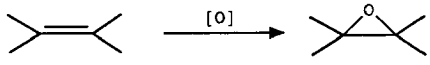



*Scheme 5.2*

An interesting feature of epoxidation chemistry is the possibility to generate chiral epoxides, thereby creating two stereogenic centers in a single operation starting with prochiral olefins. In order to perform enantioselective epoxidations, the design of chiral catalysts is a highly demanding goal[9]. At the time we started this investigation, efficient enantioselective catalytic epoxidation of olefins not bearing functional groups was unknown (vide infra). In addition to the use of dinuclear nickel(II) complexes as epoxidation catalysts we wish to take advantage of the unique possibility to perform asymmetric epoxidations, provided suitable chiral modifications of the dinuclear nickel(II) catalyst can be made. For the synthesis of these chiral complexes we made use of (S)-proline as an easily available building block that can be readily modified. In the rest of this chapter a short introduction of the catalytic conversions of alkenes to epoxides using enzyme mimics based on porphyrins and the major achievements in asymmetric epoxidation is given. Subsequently, the synthesis, structural characterization and applications of new (chiral) dinuclear copper(II) and nickel(II) complexes are described.

## 5.2 *Synthesis of epoxides*

Epoxides (Greek $\epsilon\pi i$ = close) are three-membered cyclic ethers (**510**) as shown in scheme 5.3. The combination of a strained three-membered ring and a high electron density on the oxygen atom permits a wealth of reactions making epoxides extremely important intermediates in both laboratory and industrial use[10,11]. The epoxidation reaction is also attractive in asymmetric synthesis since it can lead to building blocks containing two stereogenic centers.

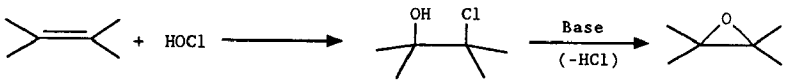



509 510

*Scheme 5.3*

In general, four basic routes to convert alkenes into epoxides are used.

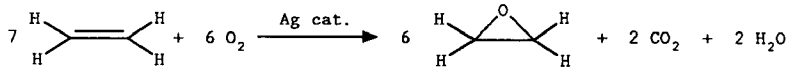
1) The chlorohydrin process. In this process an alkene is allowed to react with in situ prepared hypochlorous acid. The resulting chlorohydrin **511** is treated with a base to form epoxide and a chloride salt[11] (scheme 5.4).




509 511 510

*Scheme 5.4*

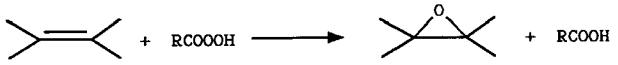
2) Direct oxidation. In this process dioxygen oxidation of an alkene with the aid of a silver catalyst gives epoxides[12] (scheme 5.5). However, this is only applicable for ethene, other alkenes are oxidized mainly to water and carbon dioxide.




509 510

*Scheme 5.5*

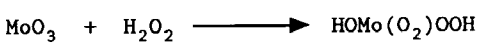
3) Oxidation by peroxy acids. Another important route involves the use of peracids RCOOOH as epoxidation agents[13] (scheme 5.6). Peroxy benzoic acid is one of the most important peracids for preparing epoxides because of its ready availability and efficiency. The introduction of electron withdrawing substituents in the peracid (as in MCPBA) increases the reaction rate, which indicates that the oxygen atom transferred in this reaction has an electrophilic character[14].




509 510

*Scheme 5.6*

4) Hydrogen peroxide / alkyl hydroperoxide routes. Many acidic metal oxides, e.g. $WO_3$, $MoO_3$, $CrO_3$, $TiO_2$ etc. and coordination complexes derived thereof catalyze the reaction of hydrogen peroxide with alkenes via the formation of inorganic peroxy acids[15] (scheme 5.7). These $H_2O_2$ oxidations have, however, often low selectivities because of the facile reaction of $H_2O_2$ with the epoxide[16]. A superior procedure uses the metal alkyl hydroperoxide system as oxidant. These systems give in some cases stereospecific reactions, for instance *cis*-alkenes giving *cis*-epoxides exclusively[17].



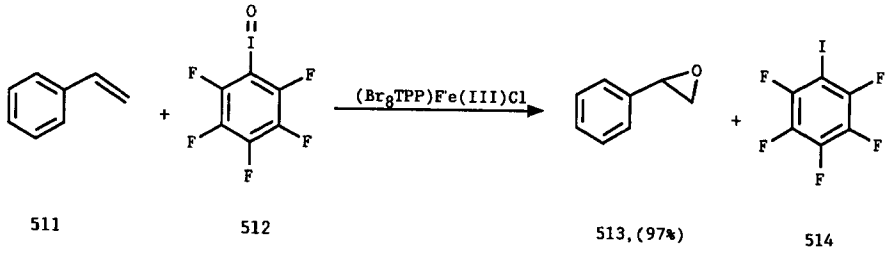

*Scheme 5.7*

The use of transition metal complexes as catalysts for epoxidations has received increased attention during the past two decades. There are a number of reasons such as the requirement for functionalization of lower alkenes formed as by-products in the manufacture of gasoline, the interest in understanding oxidations of biological importance, the need for selective oxidation and the preparation of optically active epoxides[18].

In nature, epoxidation is an important part of the metabolic transformation of a variety of substrates in order to make them biologically

active or increase the solubility and thus facilitating excretion of exogenous compounds[19]. These transformations are catalyzed by the cytochrome P450 class of enzymes and various peroxidases[20]. All these enzymes employ iron(III) porphyrins at their active sites in order to effect oxygen atom transfer to these substrates.

With the aim to mimic the cytochrome P450 function and to develop efficient and synthetically useful catalysts for epoxidation, most effort have been devoted to various metalloporphyrins. Most of the synthetic and mechanistic studies have focussed on chromium, manganese and iron complexes of porphyrins in which hydroperoxides, peracids, hypochlorite, N-oxides and iodosyl arenes are substituted for $O_2$ as terminal oxidants[3,21,25]. Groves and co-workers[22] and Chang and co-workers[23] were the first to prepare model systems consisting of iron(III) porphyrins and iodosyl benzene that were able to mimic the cytochrome P450 functions, e.g. epoxidations of alkenes and hydroxylations of alkanes. One of the best results obtained at present has been achieved by Ostovic and Bruice[24]. They synthesized the sterically hindered (meso-tetrakis (2,6-dibromophenyl)porphinato)-iron(III)chloride ($(Br_8TPP)Fe(III)Cl$) and investigated this complex in the epoxidation of nine different alkenes using $C_6F_5IO$ (**512**) as the oxygen transfer agent (scheme 5.8). Nearly quantitative yields of epoxides were obtained in all cases with catalyst turnover numbers of 100 - 200.

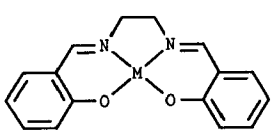



511 512 513, (97%) 514

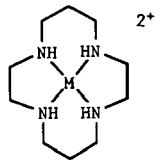
*Scheme 5.8*

Although these synthetic porphyrin model systems are now well established[25], some major disadvantages make them in practice less useful as efficient catalysts for olefin epoxidation. They are difficult to synthesize, laborious to purify and not easily modified. Their solubility is low and they are prone to ligand oxidation and N-alkylation when operative in epoxidation[24,26].

For these reasons some groups have recently reported non-porphyrin based epoxidation catalysts. Kochi and co-workers[24] investigated chromium, manganese and nickel based mononuclear complexes of salen (**515**) and cyclam (**516**) derivatives in epoxidation chemistry (figure 5.2). Most of these complexes showed reactivity patterns comparable to the TPP-iron(III) complex and thus gave reasonable activity in the catalytic oxygen transfer from iodosyl benzene to olefins. For these systems it is proposed that LNi(IV)O and LMn(V)O are the oxygen transfer agents but that they are in equilibrium with the unreactive LNi(III)ONi(III)L and LMn(IV)OMn(IV)L $\mu$-oxo dimers. These epoxidations catalysts are easy to synthesize and modifications are readily introduced (vide infra).




515, M = Ni, Mn, Cr



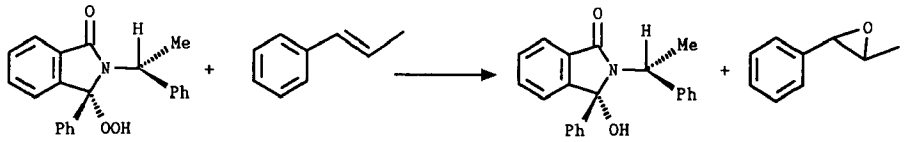

516, M = Ni

*Figure 5.2*

## 5.3 *Enantioselective epoxidations*

The enantioselective preparation of chiral epoxides is an important synthetic target in organic synthesis. However, at present no efficient methods are available to convert olefins, not bearing additional complexing sites, into pure enantiomers of epoxides. Rebek and McCready[27] described stoichiometric reactions of several chiral $\alpha$-hydroxy and $\alpha$-amino hydroperoxides (e.g. **517**)

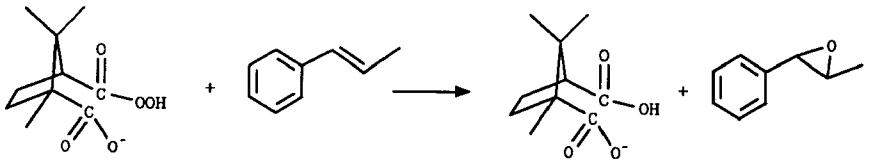
with alkenes but low e.e.'s were obtained. For example *trans*-ß-methylstyrene gave in 5.5% e.e. epoxide **520** (scheme 5.9).




517 518 519 520 30%, 5.5%ee.

*Scheme 5.9*

Pirkle and Rinaldi[28] reported stoichiometric reactions of monoperoxy camphoric acid (**521**) as a chiral oxidant for the asymmetric synthesis of epoxides. However, this oxidant is difficult to purify and low e.e.'s (≤9%) were obtained. An example is given in scheme 5.10.




521 518 522 520, 80%, 9%ee.

*Scheme 5.10*

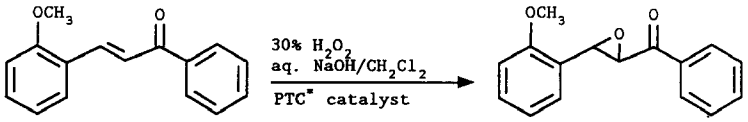
Davis and co-workers[29] found that diastereomeric 2-sulfonyl oxaziridines epoxidized unfunctionalized olefins with better selectivity than do chiral peracids or hydroperoxides. The epoxidation reaction of *trans*-ß-methylstyrene (**518**) using this oxidant gave 80% yield of the corresponding epoxide (**520**) with 27% e.e.. Modest improvements in these methods have been described.

The major disadvantage, besides the low enantioselectivity, of the methodology described above is the use of stoichiometric amounts of chiral oxidant, which are not easy to prepare. It is therefore desirable to look for a catalytic system in which a cheap oxidant is used and a chiral catalyst induces

an enantiomeric excess in the epoxide. Several examples of this concept are known but only alkenes with additional complexing sites give good results.

The discovery of the Katsuki-Sharpless reagent[30], which consists of t-BuOOH in combination with a chiral titanium tartrate catalyst, for the asymmetric epoxidations of allylic alcohols has shown the synthetic utility of this methodology. This system affords consistently high asymmetric inductions (e.e. ≥ 95%) with a wide range of prochiral allylic alcohols (see also section 1.3). However, this asymmetric epoxidation is only well applicable to allylic alcohols.

Wynberg and Marsman[31] reported the synthesis of optically active epoxy ketones (e.g. **524**) (e.e. ≤ 55%) starting from α,β-unsaturated ketones (scheme 5.11). In their phase-transfer system hydrogen peroxide is the oxidizing agent, which is transferred into the organic phase containing the substrate by means of a chiral quarternary ammonium salt derived from the cinchona alkaloid family as phase-transfer catalyst.




523 524, 90%, 55%ee.

*Scheme 5.11 (PTC* = quininium benzyl chloride)*

For the enantioselective epoxidation of unfunctionalized olefins several porphyrin based catalysts have been reported. Groves and Myers[32] reported the synthesis and use of a chiral iron porphyrin complex **525** for epoxidations of prochiral olefins, using iodosyl arene compounds as oxygen donor, to give e.e.'s ranging from 0 - 51% (figure 5.3). Several modifications of this complex were made and these complexes were found to catalyze epoxidation reactions with comparable e.e.'s. Mansuy and co workers[33] prepared a "basket handle" iron porphyrin **526**, bearing (L)-phenyl alanine residues, which catalyzed the epoxidation of alkenes giving e.e.'s in the range of 12 to 50%.

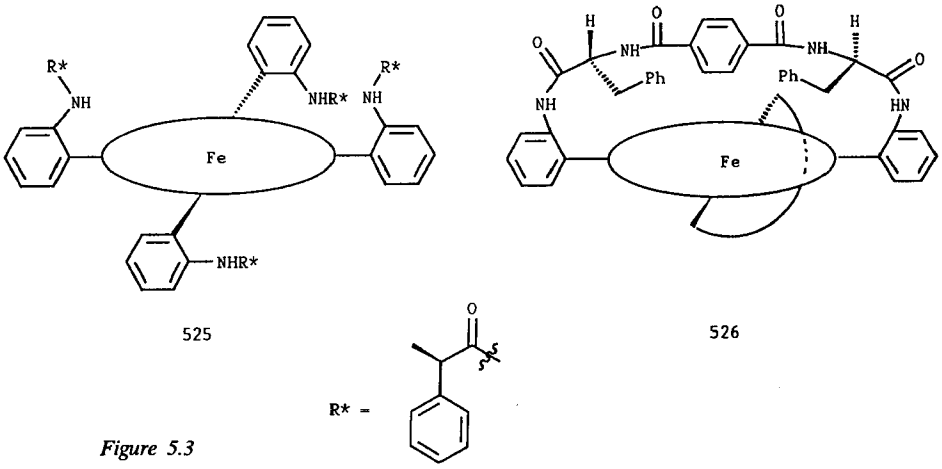
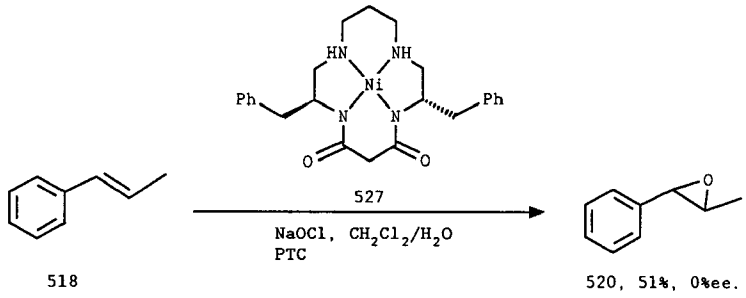



*Figure 5.3*

Although these are beautiful complexes, their preparation is extremely laborious and difficult and modifications of the ligand did not result in a substantial increase of the e.e.'s[34].

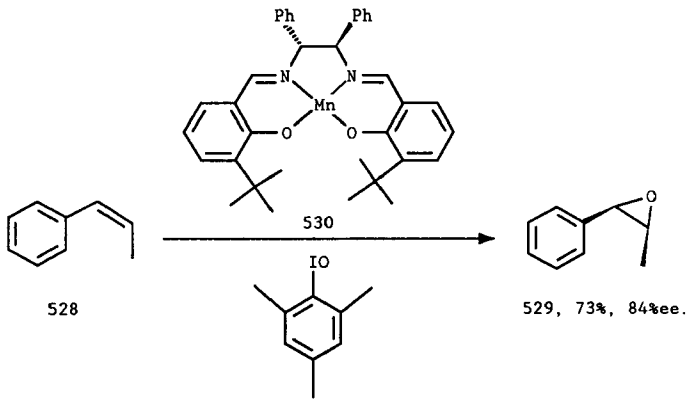
For these reasons and in order to achieve better enantioselectivities, three groups have recently investigated chiral non-porphyrin based catalysts.

Burrows and Wagler[35] reported the synthesis of an optically active dioxocyclam macrocycle **527** bearing two benzyl side change derived from phenyl alanine. Its Ni(II) complex catalyzes the oxidation of several olefins using sodium hypochlorite as the oxidant, however no asymmetric induction was found (scheme 5.12).




*Scheme 5.12*

Jacobson and co-workers[36] found, very recently, asymmetric induction in catalytic epoxidation reactions of unfunctionalized alkenes using iodosylmesitylene and a chiral salen derived manganese complex **530** as catalyst (scheme 5.13). While yields are moderate to good (50-93%), the e.e.'s are the highest reported up to now ranging from 20-93%. Especially *cis*-alkenes give high e.e.'s (78-93%).



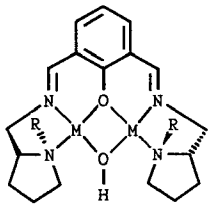

*Scheme 5.13*

This high induction is remarkable because the stereogenic centers are quite remote from the proposed metal-oxo center whereas the phenyl substituents are in a pseudo-equatorial orientation. This complex is the first example of a non-porphyrin based catalyst that is easily prepared and gives higher asymmetric induction compared to the modified porphyrin systems.

Because the use of non-porphyrin based complexes as epoxidation catalysts looked promising, we decided to prepare new chiral dinuclear nickel(II) complexes and investigate them in the epoxidation reaction.

We wanted to introduce the chirality close to the metal center. For this reason, (S)-proline, a secondary amine, was chosen as a chiral building block because of its possibility to form a stereogenic center on the nitrogen atom when coordinated via this nitrogen atom to a metal center (figure 5.4). This then creates higher asymmetry close to the metal active site of the

complex which could probably enhance the discrimination between the prochiral faces of the alkene in the formation of epoxide enantiomers.

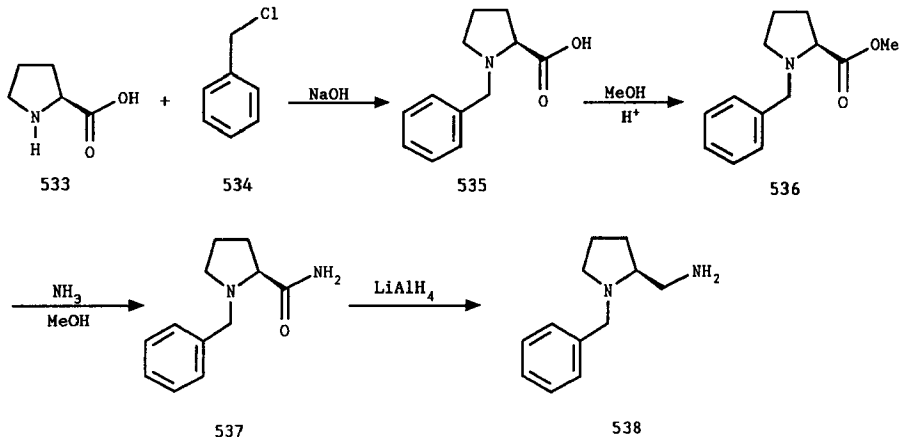


532

*figure 5.4*

## 5.4 *Synthesis of the chiral ligands*

For the preparation of the chiral ligands (S)-proline had first to be converted into a suitable bis-amine. The synthesis of (S)-1-benzyl-2-aminomethyl-pyrrolidine (**538**) is outlined in scheme 5.14.




533 534 535 536

537 538

*Scheme 5.14*

In the first step (S)-proline is N-alkylated using benzyl chloride and NaOH in 32% yield to provide the corresponding benzylated proline **535**[37]. Subsequent esterification of **535** yielded the corresponding methoxy ester **536** in 95% yield.

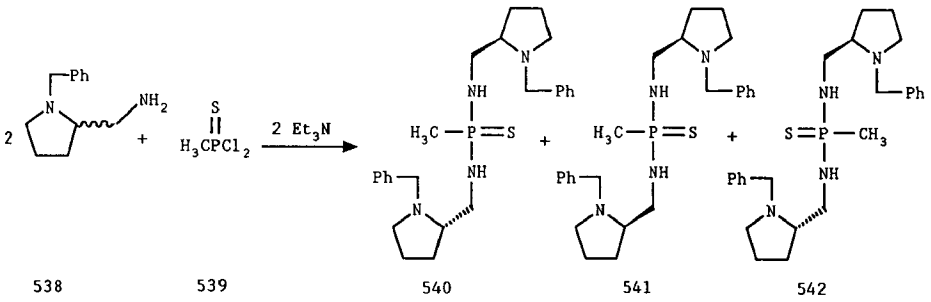
The ester **536** was converted to an amide, according to a literature procedure[38] for an analogous N-alkylated compound, by a reaction with $NH_3$ in MeOH in an autoclave at 80°C. This procedure gave amide **537** in 80% yield after crystallization. In the last step **537** was converted into a bis-amine via a $LiAlH_4$ reduction to provide after distillation **538** as a colourless oil in 80% yield.

Before proceeding further with the synthesis of the ligand it had to be established whether (partial) racemization had taken place during the synthesis of **538** following the described synthetic route. This meant the enantiomeric excess (e.e.) of **538** had to be determined.

### 5.5 *The e.e. determination of 538*

Amino acids and derivatives thereof are among the most important groups of chiral compounds and many methods have been developed to determine the enantiomeric purity of these compounds. One of the easiest method for determining the e.e. of amines has been developed recently in this laboratory by Strijtveen, Kellogg and Feringa[39]. It uses $^{1}H$ decoupled $^{31}P$-NMR spectroscopy and is based on the principle that diastereomeric derivatives of amines have different chemical shift values. In this method no chiral auxiliary is necessary for the e.e. determination of amines. Two equivalents of a chiral compound are "coupled" with an achiral reagent A to form diastereoisomers R - A - R, S - A - S and R - A - S in the case of a racemic (R, S) compound and a single diastereoisomer R - A - R (or S - A - S) in the case of enantiomerically pure material.

Two equivalents of amine **538** were reacted with one equivalent of $CH_3PSCl_2$[40] (**539**), as a coupling agent, to provide in the case of racemic amine (**538**) (which was prepared starting from racemic proline following scheme 5.14, in 21% overall yield) a 1 : 2 : 1 mixture of S - A - R, S - A - S and R - A - R, R - A - S diastereoisomers **540**, **541** and **542** (scheme 5.15). In the case of optical pure (S)-1-benzyl-2-aminomethyl-pyrrolidine (**538**) only **541** is expected.



538 539 540 541 542

*Scheme 5.15 (only one enantiomer of racemic **541** is shown for simplicity)*

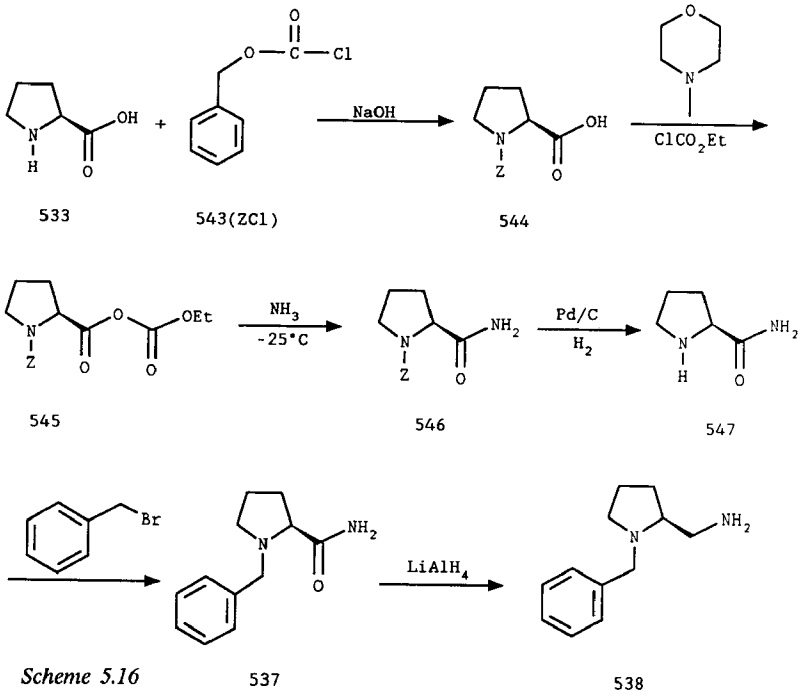
The $^{1}H$ decoupled $^{31}P$-NMR spectrum of the mixture of **540, 541** and **542** derived from racemic amine **538** showed three well separated singlets for the racemate (R, S) and two meso diastereomers with a (meso), (RR,SS) ratio of 50 : 50. The ratio of these singlets is directly related to the enantiomeric excess of the amine **538**. In the same manner a $^{31}P$ NMR spectrum of the chiral amine **538** was obtained.

To our surprise partial racemization (20%) of the amine **538** had occurred during its synthesis outlined in scheme 5.14. Probably this racemization occurs in the amide forming reaction were ester **536** is reacted with basic $NH_3$ in MeOH at 80°C during 24 h.. Base catalyzed racemization of amino esters is well precedented[41]. For this reason another procedure had to be found for the preparation of the target amine **538**.

### 5.6 *Improved synthesis of chiral diamines*

In the above described synthesis of diamine **538** the most critical step was the conversion of the carboxylic ester into the corresponding amide. We decided to introduce this functionality using much milder conditions at an early stage in the synthesis. Therefore, (S)-proline (**533**) was converted in three steps into (S)-proline amide (**547**) according to scheme 5.16. In the first step the proline amine functionality was protected by the well known Z group (Z = carbobenzoxycarbonyl) under Schotten - Baumann[42] conditions using

aqueous NaOH (2 equivalents) as the base. In the following step the carboxylic acid **544** was converted into the amide. This was achieved by a reaction of **544** with ethyl chloroformate using N-methyl morpholine as the base to provide intermediate **545** which was not isolated but converted in situ to the amide using $NH_3$ at -25°C[43]. Amide **546** could readily be purified using a basic extraction procedure to remove unreacted carboxylic acid **544**. In the third step the protective group was easily removed by hydrogenation using Pd/C and a $H_2$ atmosphere. This gave (S)-proline amide **547** in 70% overall yield from (S)-proline. In this way large quantities of (S)-proline amide (**547**) could be obtained, which was identical in all respects ($^1$H NMR, $^{13}$C NMR, m.p. and rotation) with a sample bought from Aldrich. Because of the high price of this compound we made it ourselves.




533 543(ZCl) 544

545 546 547

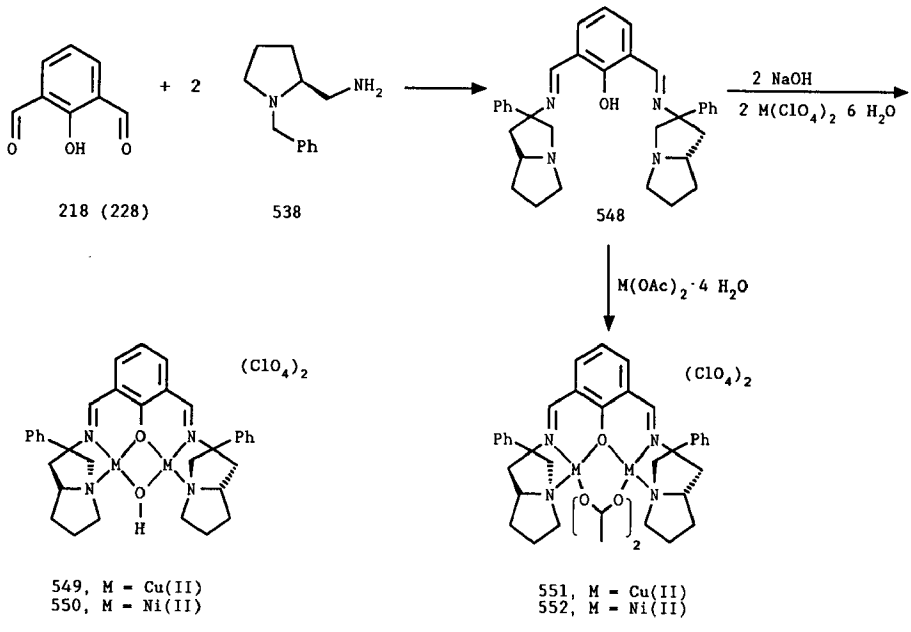
*Scheme 5.16* 537 538

Amide **547** was easily converted into its benzylated product **537** via a reaction with benzyl bromide to provide the tertiary amine amide **537** in 60% yield. In the last step **537** was reduced using $LiAlH_4$ to the bis-amine **538**. To establish

that no racemization had occurred during the synthesis of **538**, as outlined in scheme 5.16, two equivalents of **538** were reacted with one equivalent of the coupling reagent $CH_3PSCl_2$ (**539**) to provide the thio-phosphonamide **541**. The $^1H$ decoupled $^{31}P$ NMR spectrum for this adduct showed only one (singlet) signal. This indicated that bisamine **538** was obtained enantiomerically pure (see also section 5.5).

### 5.7 *Chiral dinuclear Cu(II) and Ni(II) complexes derived from 538*

With the bis-amine **538** enantiomerically pure in hand we could prepare chiral dinucleating ligands. In analogy with the ligands for the copper complexes, described in the previous chapters, a phenoxy moiety was used as a bridging group between the two metal centers. The synthesis of the dinuclear metal complexes, derived from **538**, are shown in scheme 5.17. Two equivalents of bis-amine **538** were allowed to react, in MeOH, with one equivalent of 1-hydroxybenzene-2,6-dicarboxaldehyde (**228**) to provide the bis-imine ligand **548**. This ligand was not isolated but reacted in situ with two equivalents of $M(ClO_4)_2 \cdot 6H_2O$ (M = Cu(II), Ni(II)) and two equivalents of NaOH to provide the phenoxy-hydroxy bridged dinuclear metal complexes **549** and **550** in respectively 43 and 41% yield. Compound **549** was dark green crystalline and analysis showed a bruto formula of $C_{32}H_{38}Cl_2Cu_2N_4O_{10} \cdot H_2O$. Complex **550** was red coloured and analysis showed a formula of $C_{32}H_{38}Cl_2Ni_2N_4O_{10}$. When ligand **548** was allowed to react with two equivalents of $M(OAc)_2 \cdot 4H_2O$ (M = Cu(II), Ni(II)) and one equivalent of $NaClO_4 \cdot H_2O$, dinuclear metal complexes **551** and **552** were obtained. Analysis of **551** and **552** showed a Cu/N and Ni/N stoichiometry of 1 : 2 and 2.5 : 4 respectively. An X-ray analysis of **551** revealed that no hydroxy bridge between the two metal centers is present but instead two acetate molecules are bridging the two metal ions giving five coordination around the metal centers instead of four coordination as is the case in the hydroxy bridged complexes **549** and **550** (vide infra). These different coordination spheres give rise to different physical (and



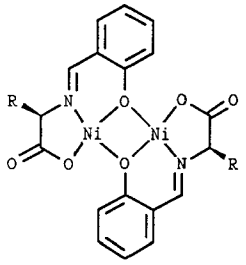

*Scheme 5.17*

chemical) properties of complexes **549**, **550** and **551**, **552**. For example, whereas **551** and **552** are very soluble in $CH_2Cl_2$/ether mixtures, complexes **549** and **550** need more polar solvents to dissolve. Another interesting aspect of these compounds is their presumed $C_2$ symmetry. We expect on steric grounds that in all complexes the two benzylic groups have a *trans* relation to each other. This means one benzyl group lies below the M - O(phenoxy) - M plane whereas the other one lies above this plane, giving a $C_2$ symmetric molecule. However, this had to be confirmed by X-ray analysis (vide infra).

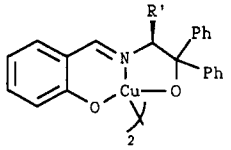
In the literature few complexes have been described in which amino acids or derivatives are condensed to Schiff bases and then allowed to react with metal salts to form dinuclear Ni(II) and Cu(II) complexes.

Theriot and co-workers[44] reported the synthesis of dimeric nickel(II) complexes derived from salicyl aldehyde and several (S)-$\alpha$-amino acids (**553**) (figure 5.5) but no structural analysis was given. Aratani[45] reported the structural characterization of a dimeric Cu(II) complex **554** derived from salicyl aldehyde and $\alpha$-amino-alcohols.

To our knowledge no chiral dinuclear Cu(II) and Ni(II) complexes are known in which the phenoxy dialdehyde (**228**) moiety serves as a bridging structural unit despite the overwhelming amount of dinuclear Cu(II) and Ni(II) complexes derived from achiral ligands, which have been fully characterized.




553




554

*Figure 5.5*

### 5.8 *Crystal and molecular structures of complexes 549, 550 and 551*

In order to establish the proposed structures of **549, 550** and **551**, X-ray analyses were undertaken. For a general introduction to Cu(II) coordination see section 2.7.

*Molecular structure of 549*

Crystallization of **549** from a $H_2O$/MeOH mixture gave green crystals which were suitable for X-ray analysis. The complex **549** crystallizes in the orthorhombic space group $P2_12_12_1$ with unit cell dimensions a = 8.870(2), b = 11.153(2) and c = 34.522(4) Å. The structure was only solved to an R index of 0.085 due to the low quality of the crystals. The molecular structure with adopted numbering scheme of **549** is given is figure 5.6. Some selected bond distances and angles are given in table 5.1. The complex adopts a $C_2$ symmetry except for the benzyl groups. One benzyl group points above the Cu(1) - O(1) - Cu(2) plane towards the phenol moiety whereas the other benzyl group, below the Cu(1) - O(1) - Cu(1) plane, points away from the

bridging phenol group. This is probably due to a packing effect which is caused by steric hindrance of the $ClO_4^-$ counter ions. It is reasonable to assume that in solution a real $C_2$ axis is present in the molecule due to the conformational mobility of the benzyl substituents. The geometry around each Cu(II) ion in **549** is slightly distorted square planar (max. deviation from mean plane is 0.19 Å) with a Cu(1) - Cu(2) separation of 2.971(3) Å, which is normal for hydroxy-phenoxy bridged dinuclear Cu(II) complexes.

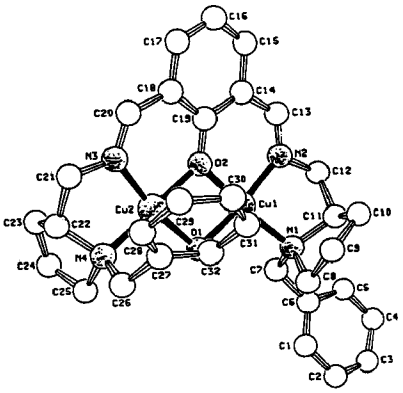



*Figure 5.6: Molecular structure with adopted numbering scheme of **549** (counter ions are omitted for clarity).*

*Table 5.1: Selected interatomic distances (Å) and angles (deg) for **549***

| | | | |
|---|---|---|---|
| Cu(1) - O(1) | 1.904(11) | O(1) - Cu(1) - O(2) | 78.5(2) |
| Cu(1) - O(2) | 1.964(11) | O(1) - Cu(1) - N(1) | 100.8(5) |
| Cu(1) - N(1) | 2.013(13) | O(1) - Cu(1) - N(2) | 168.7(5) |
| Cu(1) - N(2) | 1.916(13) | O(2) - Cu(1) - N(1) | 164.0(5) |
| Cu(2) - O(1) | 1.906(11) | O(2) - Cu(1) - N(2) | 91.3(5) |
| Cu(2) - O(2) | 1.937(11) | N(1) - Cu(1) - N(2) | 87.8(5) |
| Cu(2) - N(3) | 1.924(15) | O(1) - Cu(2) - O(2) | 78.1(5) |
| Cu(2) - N(4) | 1.994(13) | O(1) - Cu(2) - N(3) | 168.9(6) |
| | | O(1) - Cu(2) - N(4) | 102.6(6) |
| | | O(2) - Cu(2) - N(3) | 91.5(6) |
| | | O(2) - Cu(2) - N(4) | 175.1(5) |
| | | Cu(1) - O(1) - Cu(2) | 102.5(5) |
| | | Cu(1) - O(2) - Cu(2) | 99.2(5) |
| | | N(3) - Cu(2) - N(4) | 86.4(7) |

*Molecular structure of 551*

Crystallization of **551** from a $CH_2Cl_2$/ether mixture gave **551** as green crystals which were suitable for X-ray analysis. The complex crystallizes in the monoclinic space group $C_2$ with unit cell dimensions of a = 21.358(2), b = 9.454(1) and c = 10.820(1) Å. Each unit cell contained one molecule of **551**, two $CH_2Cl_2$ solvate molecules and one counter ion. The structure was solved to an R index of 0.048.

The molecular structure is depicted in figure 5.7 and selected bond distances and angles are given in table 5.2. As was expected the complex is $C_2$ symmetric. In **551** the Cu(II) ions are triple bridged by an $\mu$-phenoxo and two $\mu$-acetato moieties. These two $\mu$-acetato bridges are unexpected in view of the more usual type of mono-$\mu$-acetato copper(II) derivatives obtained with other dinucleating ligand systems[46]. The bridging acetate groups are not equally bonded to each Cu(II) ion (d (Cu - O(2)) = 2.1620(70) Å, d (Cu - O(3)') = 1.9370(70) Å), which is very akin to the distances found in a related dinuclear Cu(II) complex as was recently described by Bertoncello and co-workers[47a]. The five donor atoms around each Cu(II) ion adopt a distorted square-pyramidal arrangement such that O(1), O(3)', N(1) and N(2) form the basal plane around copper. The metal is positioned out of this plane towards the apical oxygen O(2). The Cu - Cu distance (3.2963(13) Å) is typical for $\mu$-phenoxo-bis($\mu$-acetato) bridged dinuclear metal (Fe, Mn) complexes[47b].

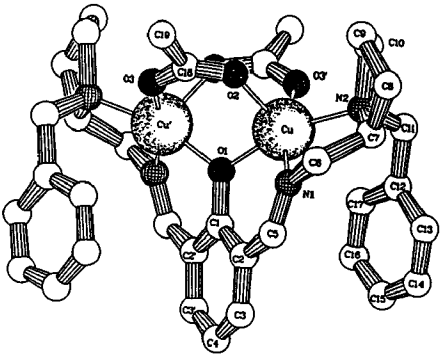


*Figure 5.7: Molecular structure with adopted numbering scheme of **551** (counter ions are omitted for clarity).*

*Table 5.2:* *Selected interatomic distances (Å) and angles (deg) for 551*

| | | | |
|---|---|---|---|
| Cu - O(1) | 1.9700(50) | O(1) - Cu - O(2) | 94.70(20) |
| Cu - O(2) | 2.1620(70) | O(1) - Cu - N(1) | 87.80(30) |
| Cu - O(3)' | 1.9370(70) | O(1) - Cu - N(2) | 163.00(30) |
| Cu - N(1) | 1.9350(70) | O(1) - Cu - O(3)' | 97.20(20) |
| Cu - N(2) | 2.0760(80) | O(2) - Cu - N(1) | 93.20(30) |
| Cu - Cu' | 3.2963(13) | O(2) - Cu - N(2) | 99.50(30) |
| | | O(2) - Cu - O(3)' | 100.10(30) |
| | | N(1) - Cu - N(2) | 82.00(30) |
| | | N(1) - Cu - O(3)' | 165.30(30) |
| | | N(2) - Cu - O(3)' | 89.60(30) |

*Nickel(II) coordination and molecular structure of 550*

In nature the most abundant oxidation state of Ni is +2, with a $d^8$ configuration, although oxidation states ranging from -1 to +4 are known. The overwhelming majority of Ni(II) complexes have coordination number four, five or six; coordination numbers of three, seven and eight are quite rare. In six coordinated complexes mostly a pseudo octahedral stereochemistry is found. The five coordinated Ni(II) complexes have structures which are generally near one of the two limiting geometries, namely the square pyramid and the trigonal bipyramid. The majority of four coordinated Ni(II) complexes are square planar and invariably diamagnetic, whereas pseudo tetrahedral complexes are rare but always paramagnetic[48].

Many dinuclear Ni(II) complexes have been prepared for several reasons. One is to mimic the active site structures and catalytic functions of Ni(II) containing enzymes such as urease. It is proposed that a dinuclear active site is present in this protein[49]. Some examples of dinuclear Ni(II) complexes are given in figure 5.8.

In order to establish the proposed structure of **550** an X-ray analysis was undertaken. Crystallization of **550** from MeOH/diisopropyl ether gave **550** as red crystalline material suitable for an X-ray analysis. The complex crystallizes in the orthorhombic space group $P2_12_12_1$ with unit cell dimensions of a = 8.788(2), b = 10.990(2), c = 34.772 Å and Z = 4.

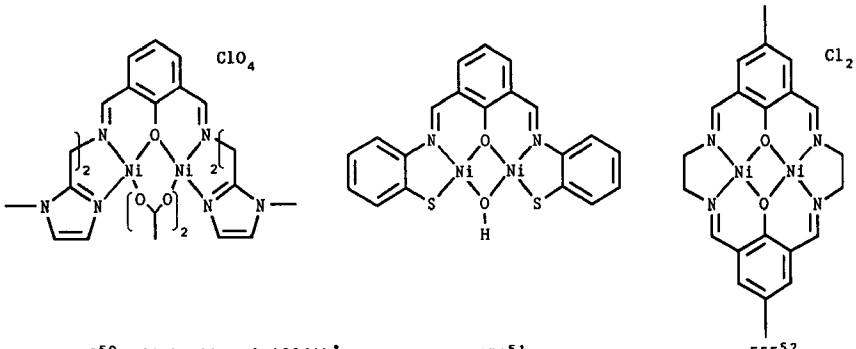



*Figure 5.8: Some selected examples of dinuclear Ni(II) complexes.*

The structure was solved to an R index of 0.056. The molecule resembles the corresponding dinuclear Cu(II) complex **549** as described before. Complex **550** has a pseudo $C_2$ axis in the crystalline state. Neither benzyl ring is related to the $C_2$ axis, which can be a packing effect due to the steric hindrance from the $ClO_4^-$ counter ions. The geometry around each Ni(II) ion in **550** is slightly distorted square planar (max. deviation from the mean plane is 0.162 Å) with a Ni - Ni separation of 2.849(1) Å, which is somewhat shorter then the Cu - Cu separation (2.97(3) Å) in **549** as was expected in view of the smaller ionic radius of Ni(II) compared to Cu(II)[53]. Some selected bond distances and angles are listed in table 5.3. Figure 5.9 shows a view along the Ni(1) - O(1) - Ni(2) - O(2) plane and, as described for the dinuclear copper(II) complex **549**, the proline and benzyl groups are in a *trans* configuration with respect to this plane.

In all three complexes **549**, **550** and **551**, we saw that the two pyrrolidine rings adopted a *trans* configuration. The configuration around each pyrrolidine nitrogen atom is tetrahedral and in this sense the nitrogen atoms have become stereogenic centers. So the large groups of the ligand are brought in an asymmetric arrangement in close proximity to the metal ions.

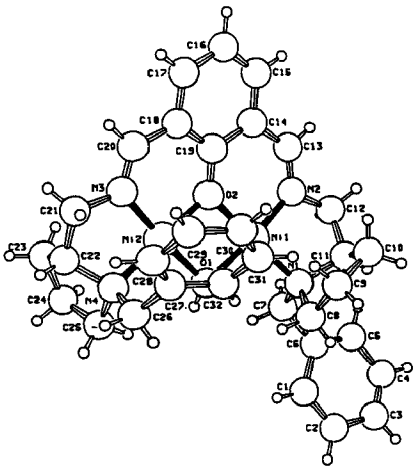



*Figure 5.9.a: Molecular structure with adopted numbering scheme of* ***550*** *(counter ions are omitted for clarity).*

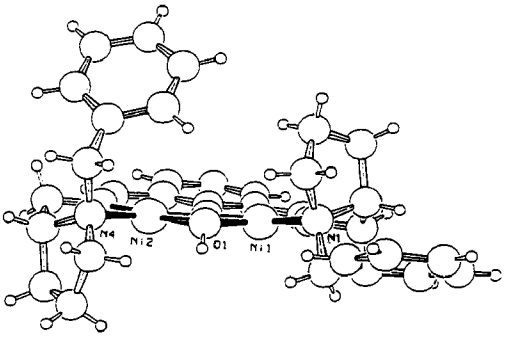



*Figure 5.9.b: A view along the Ni(1) - O(1) - Ni(2) - O(2) plane of* ***550.***

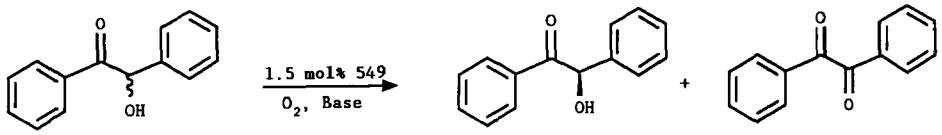
*Table 5.3* *Selected interatomic distances (Å) and angles (deg) for 550*

| | | | |
|---|---|---|---|
| Ni(1) - O(1) | 1.881(5) | O(1) - Ni(1) - O(2) | 81.0(2) |
| Ni(1) - O(2) | 1.864(5) | O(1) - Ni(1) - N(1) | 96.8(2) |
| Ni(1) - N(1) | 1.941(6) | O(1) - Ni(1) - N(2) | 175.0(2) |
| Ni(1) - N(2) | 1.826(6) | O(2) - Ni(1) - N(1) | 172.8(3) |
| Ni(2) - O(1) | 1.883(5) | O(2) - Ni(1) - N(2) | 94.0(2) |
| Ni(2) - O(2) | 1.865(5) | N(1) - Ni(1) - N(2) | 88.1(3) |
| Ni(2) - N(3) | 1.847(6) | O(1) - Ni(2) - O(2) | 81.0(2) |
| Ni(2) - N(4) | 1.928(6) | O(1) - Ni(2) - N(3) | 173.1(3) |
| Ni(1) - Ni(2) | 2.849(1) | O(1) - Ni(2) - N(4) | 97.2(3) |
| | | O(2) - Ni(2) - N(3) | 93.8(3) |
| | | O(2) - Ni(2) - N(4) | 178.0(2) |
| | | Ni(1) - O(1) - Ni(2) | 98.4(2) |
| | | Ni(1) - O(2) - Ni(2) | 99.6(2) |
| | | N(3) - Ni(2) - N(4) | 87.9(3) |

Furthermore, the pyrrolidine nitrogen metal bond distances are longer then the imine metal distances despite the fact that nitrogen amine atoms are better coordinating atoms then nitrogen imine atoms[54]. However, this is probably caused by more steric hindrance of the tri substituted amine nitrogen compared to the mono substituted imine nitrogen.

### *5.9 Dehydrogenations catalyzed by chiral dinuclear Cu(II) complex 549*

In chapter four we described that dehydrogenation reactions of $\alpha$-hydroxy ketones were catalyzed by dinuclear Cu(II) complexes. In this reaction stoichiometric quantities of base were necessary. As we have prepared and characterized chiral dinuclear Cu(II) complexes, it allows us to study catalytic asymmetric dehydrogenations. We investigated them briefly in the dehydrogenation reaction of $\alpha$-hydroxy ketones with the aim to obtain kinetic resolution of these compounds (scheme 5.18).



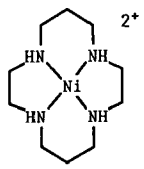

(R, S) 50% (R) 50%

*Scheme 5.18*

Several experiments were performed using benzoin as the substrate. Solvents like $CH_3OH$, $C_2H_4Cl_2$ and bases like NaOH, $NEt_3$ and Triton B, which we added slowly over longer periods, were investigated. Oxygen uptake was measured manometrically to stop the reaction at 50% conversion. In all cases no significant enrichment of one of the isomers was found. Although the precise mechanism of this oxidation is still unknown (see chapter 4), the racemization of optically pure benzoin is fast under mildly basic conditions[55]. For this reason we decided to take no further pains in attempting this resolution reaction.

### 5.10 *Epoxidation reactions catalyzed by 550 and 552*

Recently square-planar Ni(II) complexes have been of interest as catalysts for the epoxidation of alkenes using different oxidants. Kochi and co-workers[2,5a] examined a wide variety of nickel(II) complexes derived from different tetra aza-macrocycles (both neutral and anionic), Schiff bases, porphyrins and bidentate phosphines. All of these nickel(II) complexes efficiently convert iodosylbenzene as the terminal oxidant to iodobenzene. However, the conversion of olefins is restricted due to modest yields (<35%) of epoxides owing to competition from the oxidative attack on the solvent and the ligands. The most effective among these catalysts are the di-cationic Ni(II)(cyclam)$^{2+}$ (**556**) and some unsaturated analogs of this complex as well as the Schiff base derivatives Ni(II)(T-faced) (**557**) and Ni(II)(Aceted) (**558**) (figure 5.10).

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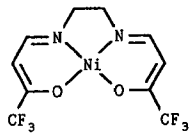


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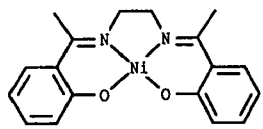



558

*figure 5.10*

Burrows and co-workers[1] investigated the oxidation of alkenes using sodium hypochlorite as the terminal oxidant and several dioxocyclam Ni(II) complexes under phase-transfer conditions (see also section 5.3). Yields of epoxides ranging from 1-51% were obtained depending on the solubility of the catalyst.

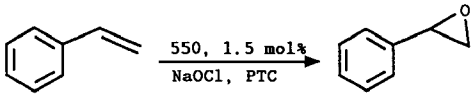
Although the role of the Ni(II) complexes in the catalysis of alkene oxidation is unclear at this moment, suggestions were made in which a dinuclear Ni(III)-oxo species is postulated as a possible intermediate (see section 5.1). With the well defined and structurally characterized dinuclear Ni(II) complexes **550** and **552** in our hands we decided to investigate these complexes on their ability as catalysts in epoxidation reactions. Three oxidation systems were looked at:

1) *Sodium hypochlorite, phase-transfer conditions*

In the first system NaOCl is used as the oxidant and the reaction takes place under phase transfer conditions using a $CH_2Cl_2/H_2O$ solvent system and benzyl triethylammonium bromide as the phase transfer catalyst (PTC). Sodium hypochlorite used under the same conditions in the presence of a transition metal catalyst has been developed extensively in the case of manganese porphyrins for the oxidation of hydrocarbons[25,26]. Complexes **550** and **552** are very soluble in solvents like $CH_2Cl_2$ and therefore we expect these complexes to operate (as catalysts) in the organic phase.

In the present solvent system $CH_2Cl_2/H_2O$ the catalyst dissolves in the organic phase, which can easy be seen because of the bright green (for **552**) and orange (**550**) colour of this phase compared to the colourless water layer. Upon addition of the oxidant these colours turn into yellow for both complexes. When styrene (1 mmol) was used as substrate in this system and 1.5 mol% of dinuclear nickel complex **550** (or **552**) was used, together with 5 mol% PTC and 2 mmol of NaOCl, we found after 16 h. of reaction time about 23% styrene epoxide while about 50% styrene was recovered (yields based on $^1$H NMR) (scheme 5.19). The remainder of the products was not

characterized but probably consists of benzoic acid and benzaldehyde which are formed by C = C bond cleavage. (The results are summarized in table 5.4).




511 513

*Scheme 5.19 (PTC = benzyl triethylammonium bromide)*

As a second substrate *trans*-stilbene was investigated using identical conditions as described for styrene. After 16 h. of reaction at room temperature, only 35% of the epoxide was obtained whereas 54% starting material was recovered. It did not make much difference which catalyst, **550** or **552**, was employed in these oxidations; both gave similar results. In addition, control experiments have shown that simple Ni(II) salts such as $Ni(OAc)_2 \cdot 4H_2O$ and $Ni(ClO_4)_2 \cdot 6H_2O$ are inactive as catalysts under these conditions and no epoxidation occurs in the absence of catalysts.

*Table 5.4: Some selected results compared to literature results*

| Catalyst | mol% | substrate | conditions[f] | conv.[a] | epox. |
|---|---|---|---|---|---|
| **550** | 1.5 | styrene | NaOCl/PTC | 50 | 23 |
| **550** | 1.5 | *trans*-stilbene | NaOCl/PTC | 46 | 35 |
| Ni(salen)[58] | 2.5 | styrene | NaOCl/PTC | 98 | 44 |
| Ni(salen)[58] | 2.5 | *trans*-stilbene | NaOCl/PTC | 80 | 46 |
| Ni(salen)[1] | 20.0 | styrene | PhIO | 99 | 26 |
| **550** | 1.5 | styrene | t-BuOOH/PTC | 50 | 3[e] |
| **550** | 1.5 | *trans*-stilbene | t-BuOOH/PTC | 75 | 65 |
| **550** | 1.5 | *trans*-ß-methylstyrene | t-BuOOH/PTC | 100 | 25 |
| **550** | 1.5 | α-methylstyrene | t-BuOOH/PTC | 100 | -[e] |
| **550** | 1.5 | Anathol | t-BuOOH/Hom. | 100 | 80 |
| - | - | Anathol | t-BuOOH/Hom. | 30 | 20 |
| **550** | 1.5 | *trans*-ß-methylstyrene | t-BuOOH/Hom. | 5 | 3 |
| Mn(TPP)Cl/Im[b59b] | 20.0 | styrene | CumOOH[c]/Hom. | 100[d] | 18 |
| Mn(TPP)Cl/Im[b] | 20.0 | *cis*-stilbene | CumOOH[c]/Hom. | 100[d] | 39 |
| Mn(TPP)Cl/Im[b] | 20.0 | *trans*-stilbene | CumOOH[c]/Hom. | 100[d] | trace |

a) Conversion based on alkene consumed
b) Im = Imidazole
c) CumOOH = $PhCMe_2OOH$
d) Conversion based on oxidant consumed
e) see text
f) PTC = phase transfer conditions: $CH_2Cl_2/H_2O$

During these oxidations of styrene and stilbene a fine black precipitate forms which is probably a nickel peroxide species (approximate formula $NiO(OH)_2$)[57]. From other studies it was shown that nickel peroxide is not an epoxidizing agent and is merely a by-product formed via the relatively facile dissociation of Ni(II) from the ligand and subsequent reaction with $OCl^-$[58]. Both styrene epoxide and *trans*-stilbene oxide were isolated and characterized by NMR and mass analysis. The epoxides were identical in all respects with samples obtained from Aldrich. They were also examined on their enantiomeric composition by $^1H$ NMR using $Eu(hfc)_3$ shift reagents. The epoxides were dissolved in 0.5 ml $CDCl_3$ and portions of the shift reagent were added as solid incrementally until a desired separation of $\alpha$ and/or ß proton signals in the $^1H$ NMR spectra of the epoxides were obtained. Integration of the fully separated enantiomeric peaks was used to determine the enantiomeric purity of the epoxide. In all cases no enrichment of one of the enantiomers was found.

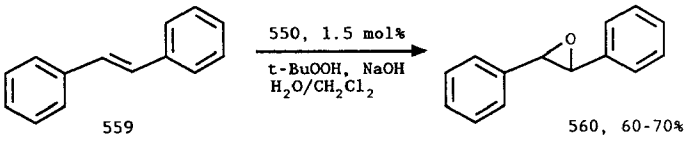
These results are comparable with the results obtained by Burrows and co-workers (see table 5.4) on hypochlorite oxidation using a salen Ni(II) complex[58] and show that dinuclear nickel(II) complexes **550** and **552** can act as catalysts in the epoxidation of alkenes using NaOCl as the terminal oxidant. However, turnover numbers are low and the catalyst is destroyed during this process. Therefore we decided to look at another oxidizing system.

2) *t-Butyl hydroperoxide, phase-transfer conditions*

The second system we looked at concerns again a phase-transfer system using $CH_2Cl_2/H_2O$ as the solvents but now the oxidant is t-butyl hydroperoxide (t-BuOOH). The results are summarized in table 5.4. No examples are known to us in which this oxidant is investigated in Ni(II) catalyzed epoxidation reactions. Only recently have epoxidations been successfully performed using this oxidant and metalloporphyrins as catalysts[59] (see also section 5.11)

*Trans*-stilbene was oxidized using 7 equivalents of t-BuOOH, 1.5 mol% of **550** and 4 equivalents of aqueous NaOH (scheme 5.20). A brightly yellow coloured solution was formed in which no precipitate (e.g. $NiO(OH)_2$) was

observed. The products were isolated after 16 h. of reaction, by a reductive working up procedure ($Na_2SO_3$) to remove excess t-BuOOH. Analysis of these products showed about 60-70% yield of stilbene epoxide (**560**), 8-10% benzaldehyde and the remainder being starting material (yields based on $^1$H NMR). Exclusively *trans*-stilbene oxide was found, no *cis* isomer was detected.

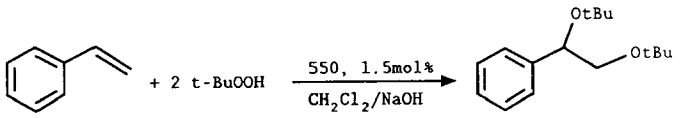



559 560, 60-70%

*Scheme 5.20*

Control experiments showed that no epoxidation was found when $Ni(ClO_4)_2 \cdot 6H_2O$ was used as a catalyst. Thus, the requirement to have ligand activated Ni(II) ions is established. Epoxidation was found not to occur when base was not added to the reaction mixture. The function of the base is probably to deprotonate the t-BuOOH. As was observed earlier for the NaOCl oxidation, little difference in product distribution was found when **552** was used as the catalyst.

Oxidation of styrene, under these conditions, gave a surprising result: besides recovered styrene and traces of benzaldehyde only 0-5% styrene oxide was formed but the major product (25%) was a di-t-butoxy substituted ethyl benzene, presumably **561** (scheme 5.21). This product could be isolated from the mixture and its structure was confirmed by $^1$H and $^{13}$ C NMR.




511 561

*Scheme 5.21*

This product is not formed through the intermediacy of styrene oxide as styrene oxide could not be converted into **561** under identical conditions.

Epoxidation of *trans*-ß-methylstyrene yielded only 20-30% epoxide while all the starting material had disappeared. TLC analysis gave a mixture of at least five products, from which the epoxide could be isolated in 12% yield by chromatography on silicagel.

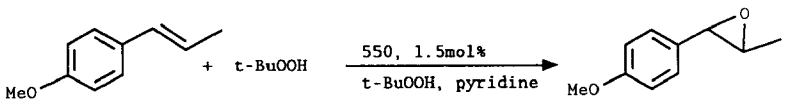
When $\alpha$-methylstyrene was used as substrate, only acetophenone was isolated in 70% yield and no epoxide was found.

All these oxidations were performed under a nitrogen atmosphere but no change in reaction products or yields was observed when oxygen was allowed to pass through the solution during the oxidations, thereby indicating free radicals are either not formed or cannot be trapped by dioxygen under the reaction conditions. A change in selectivity might be expected if radical pathways are involved.

E.S.R. measurements were performed during the oxidations but no free radicals could be detected in a temperature range from -130°C to +25°C. Addition of phase-transfer catalysts was not necessary as similar product yields and distributions were observed when no benzyl triethylammonium bromide was added. In those cases where epoxide was isolated, the reaction was investigated for the enantioselectivity of the epoxidation using $Eu(hfc)_3$ as described before or using polarimetry. In all cases no enrichment of one of the stereoisomers was found.

3) *t-Butyl hydroperoxide, homogeneous conditions*

The third system we briefly investigated using dinuclear Ni(II) complex **550** as the catalyst was a homogeneous water free one. The epoxidation reaction was performed in $CH_2Cl_2$ using three equivalents t-BuOOH in isooctane as the oxidizing agent, and two equivalents pyridine as the base. The results are summarized in table 5.4. Several substrates were investigated. Styrene did not react to a measurable extent during 48 h. using these conditions. Even *trans*-stilbene did not react. Therefore the more activated substrate *p*-methoxy-*trans*-ß-methylstyrene (anathol) (**562**) (scheme 5.22) was used. Using 1.5 mol% of **550** as the catalyst and a reaction time of 48 h., this alkene was converted into the corresponding epoxide **563** in 80% yield.




562 563

*Scheme 5.22*

In this period all starting material had disappeared and 10-15% *p*-methoxy benzaldehyde was observed as a by-product. However, when the same reaction was carried out without a catalyst under identical conditions, up to 20% of the epoxide could be detected after the same reaction time ($^1$H NMR, GCMS). Therefore addition of **550** increases the yield of epoxide but not to a great extent. When *trans*-ß-methylstyrene was used under these conditions only 2-4% epoxide was found after 48 h. of reaction. Therefore catalyst **550** is of limited value in this homogeneous system for the epoxidation of alkenes because only highly reactive (electron rich) substrates can be oxidized. The e.e. of **563** was determined, as described before using $Eu(hfc)_3$, and turned out to be less than 3%.

## 5.11 *Discussion*

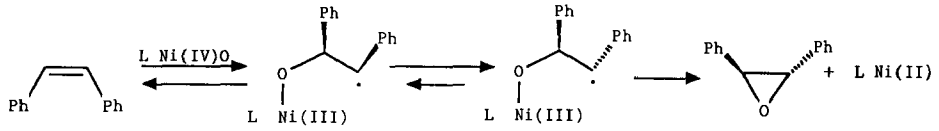
We described that bis-nickel(II) complexes **550** and **552** are catalytically active in the epoxidation reaction of various aryl-substituted alkenes. Several oxidants can be used to achieve this goal. Sodium hypochlorite gives epoxides in relative low conversions, probably due to decomposition of the catalysts. The use of t-butyl hydroperoxide under phase-transfer conditions results in higher yields but poor selectivities. The use of this same oxidant under homogeneous conditions worked only well for a highly activated substrate.

Although the active oxygen intermediates formed in these reactions are not known (see also section 5.1), a comparison can be made with the metalloporphyrins where several mechanistic studies support intermediates in the catalytic cycle. When Fe(III) and Mn(III) porphyrins are allowed to react with sodium hypochlorite, the reactive species are thought to be the metallo-

oxy species [(porphyrin$^{+\cdot}$) Fe(IV) = O][60] and [(porphyrin) Mn(V) = O][61]. The mechanistic situation becomes more complicated when alkyl hydroperoxides or $H_2O_2$ are used as oxidants. In fact these Fe- and Mn(porphyrins) are poor catalysts for the transfer of oxygen atoms from these aforementioned oxidants to alkenes. Instead these catalysts lead to fast decomposition of alkyl hydroperoxides and low epoxidation yields are obtained[62].

Two mechanisms have been proposed to explain the different nature of the oxidizing species using alkyl hydroperoxides and (porphyrin)Fe(III)Cl. The first one leads to a homolytic cleavage of the O - O bond with the formation of an alkoxy radical as the active species instead of the expected [(porphyrin$^{+\cdot}$) Fe(IV) = O] intermediate[63]. In the second, a heterolytic cleavage of the O - O bond with formation of [(porphyrin$^{+\cdot}$) Fe(IV) = O] species was proposed. In these cases the lack of efficient transfer of the oxygen atom to alkenes was explained by a faster reaction of the iron-oxo species with the alkyl hydroperoxide than with the alkene[64]. However, several recent studies have shown that the ability of Fe or Mn porphyrins to catalyze alkene epoxidation by alkyl hydroperoxides is dramatically improved by use of imidazole co-catalysts[59].

In the case of Ni(II) catalyzed epoxidation reactions using NaOCl, no intermediates have yet been isolated or otherwise unambiguously characterized. Burrows suggested a mechanism in which a LNi(IV)-oxo (L = salen) intermediate is proposed although this species might not have a structure analogous to the known LCr(V)-oxo$^+$ complex[58]. She attributed the lack of stereospecificity in the epoxidation pathway (*cis*-alkenes giving *trans*-epoxides) to subsequent formation of a Ni-oxo-olefin intermediate **566** as an open chain radical with rapid rotation around the 1,2-diphenylethane C - C bond possible before reductive elimination yields epoxides (scheme 5.23).




565 566 567 568

*Scheme 5.23*

But other intermediates, a nickel oxidant adduct or a $\mu$-oxo-Ni(III) dimer, cannot be ruled out at present[1] (see also section 5.1). A comparison of the results obtained by Burrows, using mononuclear nickel complexes, and our results by using dinuclear nickel(II) catalysts, shows that conversions are better in the former system but epoxide yields are comparable in both systems (see table 5.4). Neither system provided any enantiomeric enrichment in the epoxide.

The epoxidations carried out with t-BuOOH, as described in this chapter, represents the first example of Ni(II) catalyzed epoxidation of alkenes using this oxidant. Compared to the Fe(TPP)Cl and Mn(TPP)Cl cumyl hydroperoxide systems[59], in combination with the co-catalyst imidazole, which are able to epoxidize alkenes such as styrene and *cis*-stilbene in 18 resp. 39% yield but fail to epoxidize *trans*-stilbene, our dinuclear Ni(II) catalyst is more reactive but gives poorer selectivity in the case of styrene and ß-methylstyrene.

The formation of amounts of benzaldehyde in the epoxidation of stilbene, styrene and *p*-methoxy-*trans*-ß-methylstyrene and the formation of 70% acetophenone from $\alpha$-methylstyrene may point to a radical nature of an intermediate species in this proces because the formation of these products can be explained by trapping of these radicals by t-BuOOH[58]. However, passing oxygen through the solution had no influence on product distribution.

Hence any suggestions about the reactive intermediates operative in this epoxidation are speculative and awaits further study. *cis*-Stilbene, with respect to radical intermediates (vide infra), and, in particular cyclohexene are interesting substrates to look at as many mechanistic investigations in porphyrin catalyzed epoxidations have focused on the latter substrate giving different products for different oxidizing species[1-4,60b].

### 5.12 *Experimental part*

For general remarks see section 2.9. (S)-proline and (R,S)-proline were purchased from Janssen. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in a 10 cm cell. $MePSCl_2$ was synthesized following literature procedures[39].

**N-benzyl-(S)-proline (535)**

This compound was made following a literature procedure as described in ref. 37. Starting from 9.2 g (0.08 mol) (S)-proline (**533**), 5.3 g (32%) of **535** was obtained as a white solid. m.p. 163.7-165.7°C, $[\alpha]^{589}_{18}$ = -26.9° (C 1.0, $C_2H_5OH$) (lit. m.p. 164-165°C, $[\alpha]^{589}_{18}$ = -28.4° (C 1.0, $C_2H_5OH$)); $^1$H NMR ($CDCl_3$): $\delta$ 1.70-2.00 (m, 2H), 2.07-2.28 (m, 2H), 3.77 (m, 1H), 3.53-3.63 (m, 1H), 4.18 (dd, $J$ = 50 Hz, $J$ = 12 Hz, 2H), 7.20-7.40 (m, 5H), 8.20 (br s, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.67, 28.72, 53.13, 57.56, 67.48, 128.86, 129.19, 130.32, 130.69, 170.85 ppm.

**N-benzyl-(S)-proline methylester (536)**

To 3.6 g (18 mmol) **535** was added 50 ml aqueous HCl (1 N) and this mixture was evaporated to dryness. This procedure was repeated once more. All the remaining water was stripped off by MeOH (2 x 25 ml) and the residue was dissolved in 50 ml MeOH. Concentrated $H_2SO_4$ (1 ml) was added and the solution was refluxed for 16 h.. Next, the mixture was poured into 200 ml of a 1 N $NaHCO_3$ solution and the resulting layer was extracted with chloroform (3 x 50 ml). The chloroform layers were combined, washed with 25 ml water, dried on $MgSO_4$ and evaporated to dryness. This gave an oil which was distilled (at 130°C, 1 mm Hg) using Kugelrohr equipment to yield 2.4 g (61%) of **536** as a colourless oil. $[\alpha]^{589}_{18}$ = -85.7° (C 4.0, $CHCl_3$); $^1$H NMR ($CDCl_3$): $\delta$ 1.65-2.15 (m, 5H), 2.35 (m, 1H), 2.97-3.06 (m, 1H), 3.16-3.25 (m, 1H), 3.59 (s, 3H), 3.68 (dd, $J$ = 95 Hz, $J$ = 13 Hz, 2H), 7.15-7.30 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.74, 29.12, 51.43, 53.02, 58.48, 65.01, 126.82, 127.89, 128.96, 137.96, 174.25 ppm. Analysis calculated for $C_{13}H_{17}NO_2$: C: 71.23, H: 7.76, found C: 70.99, H: 7.79.

**N-benzyloxycarbonyl-(S)-proline (544) (Z-(S)-proline)**

This compound was prepared according to a literature procedure[42]. Starting from 57.0 g (0.5 mol) (S)-proline (**533**), 99.6 g (80%) Z-(S)-proline (**544**) was isolated as a colourless oil which crystallized upon standing in a desiccator over $P_2O_5$. $^1$H NMR ($CDCl_3$): $\delta$ 1.80-2.30 (m, 4H), 3.40-3.64 (m, 2H), 4.32-4.45 (m, 1H), 5.05-5.12 (m, 2H), 7.20-7.38 (m, 5H), 10.70 (br s, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 23.07, 23.89, 29.36, 30.49, 46.21, 46.60, 58.38, 58.87, 66.84, 66.99, 127.18, 127.30, 127.45, 127.64, 128.00, 128.09, 136.00, 154.28, 155.07, 176.26, 176.84 ppm.

**N-benzyloxycarbonyl-(S)-prolinamid (546)**

A solution of 50 g (0.2 mol) **544** in 300 ml $CH_2Cl_2$ was cooled to 0°C. There was added 21.0 g (0.21 mol) N-methyl-morpholine at such a rate that the temperature did not rise above 5°C. The resulting mixture was cooled to -15°C and next 22.8 g (0.21 mol)

ethylchloroformate, dissolved in 50 ml $CH_2Cl_2$, was added at such a rate that the temperature did not rise above -15°C. After stirring for 2 h. at -15 to -20°C the solution was cooled to -25°C. Subsequently, gaseous $NH_3$ was lead through the solution during 1 h. at such a rate that the temperature did not exceed -20°C. Stirring was continued for another hour during which time the temperature was allowed to rise to 0°C. Next the solution was poured into 200 ml $H_2O$ and the layers were separated. The $CH_2Cl_2$ layer was washed successively with 1 N HCl (2 x 50 ml), 1 N $NaHCO_3$ (2 x 50 ml) and brine (1 x 50 ml). After drying on $Na_2SO_4$ the solvent was evaporated in vacuo to yield 44 g (88%) of **545** as a colourless oil which crystallized upon standing in a desiccator over $P_2O_5$. $^1$H NMR ($CDCl_3$): $\delta$ 1.83-2.37 (m, 4H), 3.40-3.58 (m, 2H), 4.26-4.38 (m, 1H), 5.07-5.20 (m, 2H), 5.74 (br s, 1H), 7.25-7.45 (m, 5H), 7.75 (br s, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 23.44, 24.26, 28.75, 30.94, 46.79, 47.18, 58.26, 60.00, 60.28, 66.99, 126.32, 127.51, 127.79, 128.25, 128.92, 130.47, 133.25, 136.15, 174.39, 175.13 ppm.

**(S)-Prolinamid (547)**

A mixture of 10 g (0.04 mol) **546** and 100 mg 5% Pd/C in 100 ml $CH_3OH$ was shaken for 5 h. in a Parr-apparatus under a $H_2$ atmosphere. After this time the Pd/C was filtered using a celite filter aid and the methanol was evaporated in vacuo to yield 4.0 g (87%) of (S)-prolinamid **547** as white crystalline material after recrystallization from toluene. m.p. 94.6-96.2°C (lit. 95-97°C[65]), $[\alpha]^{589}_{20}$ = -99.5 (C 2.0, $CH_3CH_2OH$), (lit $[\alpha]^{589}_{20}$ = -100.0 (C 2.0, $CH_3CH_2OH$)). $^1$H NMR ($CD_3OD$): $\delta$ 1.90-2.05 (m, 3H), 2.28-2.41 (m, 1H), 3.06-3.16 (m, 1H), 3.17-3.27 (m, 1H), 3.83-3.90 (m, 1H); $^{13}$C NMR ($CD_3OD$): $\delta$ 26.89, 32.17, 47.92, 61.32, 179.34 ppm.

**N-benzyl-(S)-prolinamid (537)**

A solution of 5.7 g (50 mmol) (S)-prolinamid **547** and 8.55 g (50 mmol) benzyl bromide in 50 ml $CH_2Cl_2$/MeOH (4 : 1) was stirred for 16 h.. After this time the solvent was removed in vacuo and the residue dissolved in $CH_2Cl_2$ (100 ml). The $CH_2Cl_2$ layer was washed with aqueous 1 N $NaHCO_3$ (2 x 50 ml), $H_2O$ (50 ml) and dried over $MgSO_4$. Filtration and evaporation of the solvent in vacuo yielded a colourless oil which was distilled using a Kugelrohr apparatus. The fraction that was obtained at 160°C/0.05 mm Hg was collected and the oil solidified upon standing. This gave 6.7 g (66%) of **537** as white crystalline material. m.p. 61.1-62.7°C, $[\alpha]^{589}_{20}$ = -81.4° (C 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ 1.65-1.78 (m, 2H), 2.11-2.34 (m, 2H), 2.82-2.96 (m, 1H), 2.92-3.00 (m, 1H), 3.08-3.17 (m, 1H), 3.66 (dd, $J$ = 155 Hz, $J$ = 14 Hz, 2H), 6.94 (br s, 1H), 7.17-7.35 (m, 6H); $^{13}$C NMR ($CDCl_3$): $\delta$ 23.68, 30.24, 53.35, 59.36, 67.05, 126.84, 128.06, 128.31, 138.20, 178.18 ppm. HRMS calculated for $C_{12}H_{16}N_2O$: 204.126, found: 204.124. Analysis calculated for $C_{12}H_{16}N_2O$: C: 70.58, H: 7.84, N: 13.73, found C: 70.42, H: 8.06, N: 13.68.

**(S)-1-benzyl-2-aminomethyl-pyrrolidine (538)**

A solution of 8.0 g (39 mmol) **537** in 50 ml THF was added, under a nitrogen atmosphere, to a suspension of 4.0 g (105 mmol) $LiAlH_4$ in 100 ml THF. This mixture was refluxed for 16 h. after which time it was cooled to 10°C. Next, 6 ml 10% aqueous KOH was carefully added and the resulting mixture was refluxed for another hour until the precipitated salts were white (not grey!) coloured. After cooling to room temperature, the THF was removed from the salts by filtration over a glass filter and the salts were again refluxed for one hour with 100 ml THF and 2 ml $H_2O$. After removing the salts again by filtration, the THF layers were combined and dried over $Na_2SO_4$. Filtration and evaporation in vacuo gave a colourless oil which was distilled (at 150°C, 0.3 mm Hg) using Kugelrohr equipment to yield 6.0 g (81%) of **538** as a colourless oil. $^1$H NMR ($CDCl_3$): $\delta$ 1.28 (br s, 2H), 1.54-1.70 (m, 3H), 1.79-1.90 (m, 1H), 2.14 (m, 1H), 2.43-2.54 (m, 1H), 2.61-2.76 (m, 2H), 2.85-2.93 (m, 1H), 3.57 (dd, $J$ = 204 Hz, $J$ = 13 Hz, 2H), 7.13-7.34 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.74, 27.71, 43.92, 54.32, 58.81, 65.28, 126.61, 127.91, 128.40, 139.60 ppm. HRMS calculated for $C_{12}H_{18}N_2$: 190.147, found 190.146.

Racemic **538** was prepared starting from racemic proline via the same above described procedures. This gave overall 21% yield of racemic **538** pure according to $^1$H and $^{13}$C NMR.

**e.e. Determination of 538**

To a stirred solution of 1 mmol of primary amine **538** and 1.0 mmol of triethylamine in 2 ml $CDCl_3$ was added at -20°C a solution of 0.5 mmol $CH_3P(=S)Cl_2$ (**539**) in 1 ml of $CDCl_3$. After being stirred for 10 min., the solution was transferred into a NMR tube and the $^1$H decoupled $^{31}$P NMR spectrum was recorded. This gave for racemic **538** three singlets at $\delta$ 66.43, 66.40 and 66.19 ppm respectively in a ratio of 1 : 2 : 1 whereas for optical pure **538**, obtained via the route described in scheme 5.16, a singlet at 66.40 ppm was found.

**$\mu$-Di-acetato-$\mu$-[2,6-bis[N-((S)-1-benzyl-2-yl-pyrrolidine)-formimidoyl]phenolato]biscopper(II) monoperchlorate (551)**

A solution of 150 mg (1.0 mmol) dialdehyde (**228**) and 380 mg (2.0 mmol) (S)-1-benzyl-2-aminomethyl-pyrrolidine (**538**) in 50 ml of MeOH was stirred for one hour at room temperature. Next, 435 mg (2 mmol) $Cu(OAc)_2 \cdot 2H_2O$ was added and the resulting mixture was refluxed for 2.5 h.. After this time, 114 mg (1 mmol) $NaClO_4 \cdot H_2O$ was added and refluxing was continued for 1 h.. The solvent was evaporated in vacuo and the green solid material was crystallized from aqueous EtOH to yield 425 mg (51%) of **551** as green crystals which were suitable for X-ray analysis. Analysis calculated for $C_{36}H_{43}ClCu_2N_4O_9$: C: 51.60, H: 5.13, Cl: 4.24, Cu: 15.16, N: 6.68, found: C: 51.31, H: 5.16, Cl: 4.37, Cu: 15.11, N: 6.50.

**μ-Hydroxo-μ-[2,6-bis[N-((S)-1-benzyl-2-yl-pyrrolidine)-formimidoyl]phenolato]biscopper(II)bis perchlorate (549)**

A solution of 150 mg (1.0 mmol) dialdehyde **228** and 380 mg (2.0 mmol) (S)-1-benzyl-2-aminomethyl-pyrrolidine (**538**) in 50 ml MeOH was stirred for one hour. Next, 80 mg (2.0 mmol) NaOH and 741 mg (2.0 mmol) $Cu(ClO_4)_2 \cdot 6H_2O$ were added and the mixture was refluxed for 2.5 h.. Slow cooling of the resulting mixture yielded 370 mg (43%) of pure **549** as dark green needles, suitable for an X-ray analysis. Analysis calculated for $C_{32}H_{38}Cl_2Cu_2N_4O_{10} \cdot H_2O$: C: 44.96, H: 4.68, Cl: 8.31, Cu: 14.87, N: 6.55, found: C: 44.84, H: 4.50, Cl: 9.13, Cu: 14.76, N: 6.48.

**μ-Hydroxo-μ-[2,6-bis[N-((S)-1-benzyl-2-yl-pyrrolidine)-formimidoyl]phenolato]bisnickel(II) bisperchlorate (550)**

This complex was prepared following the same procedure as described for **549** but using 732 mg (2.0 mmol) $Ni(ClO_4)_2 \cdot 6H_2O$ instead of $Cu(ClO_4)_2 \cdot 6H_2O$. It provided 640 mg (80%) of an orange solid after precipitation from a $CH_2Cl_2$/ether solvent mixture. This material was crystallized by diffusion crystallization from a methanol/diisopropyl ether bilayer system to give 329 mg (41%) red-orange crystalline material consisting of pure **550** suitable for X-ray analysis. Analysis calculated for $C_{32}H_{38}Cl_2N_4Ni_2O_{10}$: C: 46.48, H: 4.63, Cl: 8.57, N: 6.77, Ni: 14.19, found: C: 46.31, H: 4.62, Cl: 8.42, N: 6.74, Ni: 14.06.

**μ-Di-acetoxy-μ-[2,6-bis[N-((S)-1-benzyl-2-yl-pyrrolidine)-formimidoyl]phenolato]bisnickel(II) monoperchlorate (552)**

This complex was prepared following the same procedure as described for **551** but using 430 mg (2.0 mmol) of $Ni(OAc)_2 \cdot 4H_2O$. The solvent was evaporated in vacuo and the green residue was crystallized from an ethanol/$H_2O$ mixture to yield 380 mg (46%) of a green solid which did not give satisfactory elemental analysis probably due to the presence of $Ni(ClO_4)_2$ and ethanol in the precipitate. Analysis calculated for $C_{36}H_{43}ClN_4Ni_2O_9 \cdot (C_2H_5OH)_{1.0}(Ni(ClO_4)_2)_{0.5}$: C: 45.50, H: 5.02, N: 5.58, Ni: 14.62, found: C: 44.85, H: 4.91, N: 5.52, Ni: 14.33.

**Crystal structure determination of complex 549**

The X-ray determination was performed at 130 K with MoK$\alpha$ radiation ($\lambda$ = 0.7107 Å) on a Nonius CAD4F computer controlled kappa axis diffractometer equipped with a graphite monochromator and interfaced to a PDP11/23. No suitable single-crystal was found. The crystal, having approximate dimensions of 0.20 x 0.25 x 0.35 mm, is therefore of moderate quality showing satellite reflections. The orthorhombic $P2_12_12_1$ cell parameters and volume are: a = 8.870(2), b = 11.153(2), c = 34.522(4) Å and V = 3415.2 $Å^3$. For Z = 4

and FW = 836.67, the calculated density is 1.627 g $cm^{-3}$. From a total of 6568 unique reflections in the range $1° \leq \Theta \leq 32°$, 3049 had intensities with $I \geq 2.7\ \sigma(I)$. Block-diagonal least-squares of F, with unit weights, converged to a final R = 0.085 and $\omega R$ = 0.098 respectively, using anisotropic thermal parameters for the non H-atoms and isotropic fixed thermal parameters (B = 4 $Å^2$) for the H-atoms. Selected bond distances and angles are given in table 5.1.

**Crystal structure determination of 550**

The single crystal X-ray determination was performed at 130 K with MoK$\alpha$ radiation ($\lambda$ = 0.7107 Å) on a Nonius CAD4F computer controlled kappa axis diffractometer equipped with a graphite monochromator and interfaced to a PDP11/23. A suitable crystal of the title compound, having approximate dimensions of 0.52 x 0.25 x 0.20 mm, crystallized in the orthorhombic space group $P2_12_12_1$ with a = 8.788(2), b = 10.990(2), c = 34.772(3) Å and V = 3358.3 $Å^3$. For Z = 4 and FW = 827.01, the calculated density is 1.636 g $cm^{-3}$. From a total of 5419 reflections in the range $1° \leq \Theta \leq 30°$, a number of 4112 reflections had intensities with $I \geq 3.0\ \sigma(I)$ and were used in the refinements. Block-diagonal least-squares of F, with unit weights, converged to a final R = 0.056 and $\omega R$ = 0.064 respectively, using anisotropic thermal parameters for the non H-atoms and isotropic fixed thermal parameters (B = 5.0 $Å^2$) for the H-atoms. Selected bond distances and angles are given in table 5.3.

**Epoxidation reaction - general remarks**

Domestic bleach (Piek) was used for the preparation of NaOCl solutions and was titrated before use by iodometric methods. Aqueous t-BuOOH (70%) and t-BuOOH (3 M) in isooctane were purchased from Aldrich and analyzed by titration following a procedure described in ref. 66. Chemical yields are given on bases of $^1H$ NMR analysis. The epoxides were isolated and purified by flash chromatography on silica ($CH_2Cl_2$/hexane mixtures). In the cases where styrene oxide, *trans*-stilbene oxide and *p*-methoxy-*trans*-styrene oxide were isolated, they were identical to authentic samples purchased from Aldrich and Duphar ($^1H$, $^{13}C$ NMR). Other epoxides were characterized by $^1H$ and $^{13}C$ NMR. The degree of asymmetric induction was determined by $^1H$ NMR with the chemical shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) ($Eu(hfc)_3$). The oxides obtained were dissolved in 0.5 ml $CDCl_3$ and portions of the shift reagent were added as solid incrementally until a desired separation of $\alpha$ and/or ß proton signal in the $^1H$ NMR spectra of the epoxide was obtained. Integration of the fully separated enantiomeric peaks was used to determine the enantiomeric purity of the epoxide.

**Epoxidation of alkenes using NaOCl and 550 (typical procedure)**

To a solution of 1 mmol of the alkene, 12 mg **550** (1.5 mol%) and 30 mg benzyl triethyl ammonium bromide in 10 ml $CH_2Cl_2$ was added 3 ml NaOCl (±1.2 mmol) and 7 ml $H_2O$. This mixture was stirred vigorously for 20 h. at room temperature after which period a fine black precipitate was observed. The layers were separated and the organic layer was washed two times with $H_2O$. Drying of the $CH_2Cl_2$ layer on $MgSO_4$, filtration and evaporation in vacuo yielded a mixture of products which was analyzed by $^1H$ NMR.

In a typical example 70 mg (40%) of *trans*-stilbene oxide could be obtained pure (according to $^1H$ and $^{13}C$ NMR) starting from 180 mg stilbene. The e.e. of styrene oxide was determined as described before by $^1H$ NMR; a ratio of the separated peaks of approximately 50 : 50 was found. The optical purity of *trans*-stilbene oxide was measured by using a polarimeter; however no rotation was observed.

**Epoxidation of alkenes using aqueous t-BuOOH (70%) and 550 (typical procedure)**

To a solution of 1 mmol of alkene and 12 mg (1.5 mol%) **550** dissolved in 10 ml $CH_2Cl_2$ was added a mixture of 100 mg NaOH and 1 ml t-BuOOH solution (appr. 7 mmol) in 9 ml $H_2O$. This mixture was stirred vigorously for 20 h. after which time the layers were separated. The $CH_2Cl_2$ layer was washed two times with 10 ml 1 M $Na_2SO_3$/NaOH to remove the excess peroxide. Drying of the $CH_2Cl_2$ layers over $MgSO_4$, filtration and evaporation to dryness yielded mixtures of products which were analyzed by $^1H$ NMR. Data are summarized in table 5.4. From these mixtures, epoxides were isolated by chromatography. In the case of styrene however, no epoxide was formed but instead a di-tertiar-butoxy substituted ethyl benzene **561** was obtained in 11% isolated yield. $^1H$ NMR ($CDCl_3$): $\delta$ 1.23 (s, 9H), 1.25 (s, 9H), 4.08 (dd, $J$ = 4.0 Hz, $J$ = 12.0 Hz, 1H), 4.23 (dd, $J$ = 8.0 Hz, $J$ = 12.0 Hz, 1H), 5.21 (dd, $J$ = 8.0 Hz, $J$ = 4.0 Hz, 1H), 7.24-7.38 (m, 5H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 26.21, 26.27, 76.69, 80.32, 80.47, 83.19, 126.86, 127.75, 128.09, 138.46 ppm.

When this product was analyzed by GCMS (injection temperature 160°C) styrene oxide, benzaldehyde and t-BuOH were the decomposition products of this material. In all other cases quantitative isolation of the epoxides proved to be difficult but pure samples of stilbene oxide and *trans*-ß-methyl-styrene oxide were obtained chromatography pure according to $^1H$ NMR. (**520**) $^1H$ NMR ($CDCl_3$): $\delta$ 1.35 (d, $J$ = 5 Hz, 3H), 2.94 (dq, $J$ = 5 Hz, $J$ = 2 Hz, 1H), 3.47 (d, $J$ = 2 Hz, 1H), 7.12-7.27 (m, 5H).

**Epoxidation of alkenes using t-BuOOH (3 M) in isooctane (typical procedure for homogeneous epoxidation)**

A mixture of 1 mmol alkene, 1.5 mol% **550**, 0.1 ml pyridine and 1 ml 3 M t-BuOOH in isooctane in 10 ml $CH_2Cl_2$ was stirred for 48 h. at room temperature. Styrene

and stilbene were recovered quantitatively after 48 h. of reaction. Only *p*-methoxy-*trans*-ß-methylstyrene gave a good yield (80%) of epoxide, whereas 15% *p*-methoxy-benzaldehyde could be detected. Pure *p*-methoxy-*trans*-ß-methyl-styrene-oxide could be isolated in 60% overall yield by chromatographic methods.

This product was analyzed with $Eu(hfc)_3$ to be racemic. A reaction under similar conditions without catalyst yielded only 20% ($^1H$ NMR based yield) of the epoxide after 48 h. of reaction.

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# CHAPTER 6

## MODIFIED CHIRAL BIS NICKEL(II) COMPLEXES SYNTHESIS, STRUCTURE AND ELECTRO CHEMICAL PROPERTIES

### 6.1 *Introduction*

In the previous chapter we described the synthesis and reactivity of new chiral dinuclear nickel(II) complexes. We observed moderate activity in epoxidation reactions of aryl substituted olefins but no asymmetric induction was found. If we try to rationalize these findings in terms of the molecular structure of the complexes involved there are certain aspects of prime importance:

In the first place we found that the catalytic activity decreases after 20 h. of reaction. This probably means that the catalyst does not survive the reaction conditions and decomposes, although competitive product inhibition or possible formation of inactive $\mu$-1,2-oxo species (see also section 1.2) cannot be excluded.

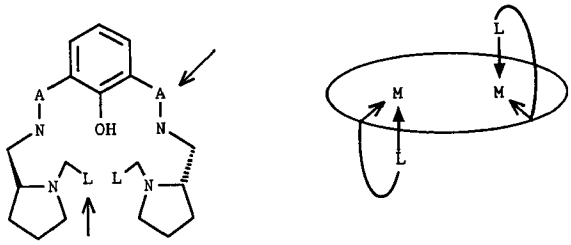



*Figure 6.1: Ligand modification (A = CH, $CH_2$, CO) and additional coordinating ligand (L = pyridyl).*

If the structure, as shown in figure 6.1 (A = CH), is considered, it is plausible that the weakest structural moiety, under aqueous phase-transfer conditions, is the imine functionality. This assumption is strengthened by the fact that at moderately acidic pH, the imine bond hydrolyses rapidly as was shown in chapter 2 and 3. Therefore it could be important to increase the

catalyst stability by replacing this functionality by a more robust unit, for example an amide (A = CO) or amine (A = $CH_2$) functionality, which does not hydrolyse so easily under the reaction conditions used.

A second point of interest is the number of coordinating groups attached to the Ni(II) nuclei. There is substantial experimental support now to assume that in the epoxidation process higher oxidation states of nickel are formed, such as a Ni(IV)-oxo, a $\mu$-1,2-oxo-Ni(III) or another nickel oxygen intermediate[1]. Higher oxidation states of Ni(II) require ligands with high electron density and one or more negative charges in order to allow for some charge delocalization from the ligand to the metal[2]. By comparison in the Mn(III)porphyrin-catalyzed epoxidation reactions additional axial ligands, such as pyridine or imidazole, substantially increase the activity of the catalyst[3]. This charge delocalization due to (coordinative) bond formation should, however, not be so large as to give rise to ligand oxidation.

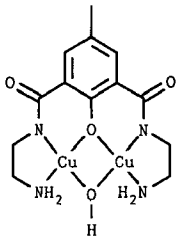
Both Ni(III) and Ni(IV) complexes are usually found in octahedral environments. Less common geometries are the square planar and the trigonal bipyramidal ones. For these reasons it might be necessary to add an additional coordinating group in our ligand, in order to stabilize higher oxidation states of nickel. If we look at the structure in figure 5.9 (p. 131), the benzyl groups could be replaced by a coordinating moiety, for example a pyridine ring. This replacement might have the additional effect of creating more sterically crowded Ni(II) nuclei which could favor a higher chiral discrimination between the $\pi$-faces of the prochiral olefins in the formation of the epoxides. Therefore the synthesis of modified ligands will be directed towards: 1) the replacement of the imine functionalities and 2) the introduction of one additional coordinating ligand for each Ni center.

## 6.2 *Modified ligand systems and complexes thereof*

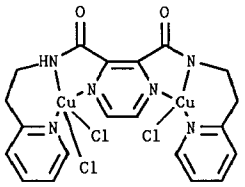
### 6.2.1. *Replacement of the imine groups*

As a consequence of the replacement of the imine functionalities in

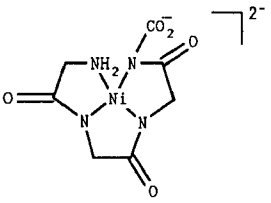
**548** it was decided first to introduce amide units, these being rather robust chemical functionalities. Amides are known to be reasonable coordinating ligands (vide infra). A prerequisite for amide coordination, however, is the presence of other coordinating groups (anchors) in the rest of the molecule[4]. In the ligand that will be described here, a phenoxy bridge and a tertiary amine functionality are present as additional anchors. The exact mode of coordination of an amide can be directed in two ways: Amide oxygen coordination can be achieved in neutral amides whereas in deprotonated amides the amide nitrogen will coordinate preferentially[5]. Many organometallic complexes have been synthesized and characterized in which the amide coordinating functionality is present. Some examples of dinuclear complexes are given in figure 6.2.




601[6]




602[7]



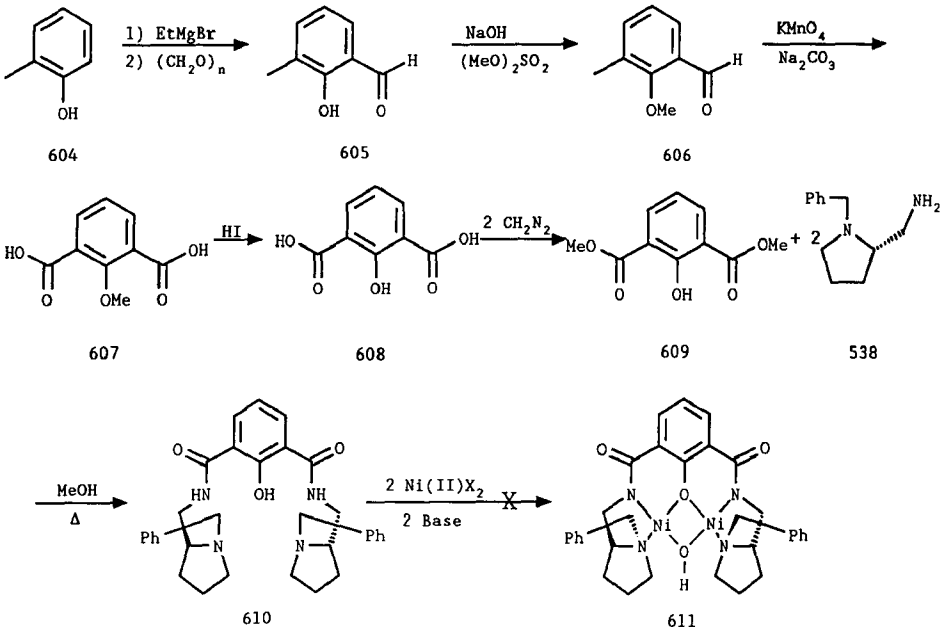

603[8]

*Figure 6.2*

The synthesis of the target ligand **610**, containing two amide units, is outlined in scheme 6.1. The synthesis of 1-hydroxybenzene-2,6-dicarboxymethyl (**609**) was executed according to known literature procedures[9-12].

In the first step *o*-cresol (**604**) is formylated using ethylmagnesium bromide and *p*-formaldehyde to provide **605** in 60% yield after distillation[9]. Before oxidizing the aldehyde and methyl substituent into the 2,6-dicarboxylic groups as in **607**, the phenol group had to be protected. This was easily done by reaction of **605** with aqueous NaOH and dimethyl sulfate[10]. Subsequent oxidation of **606** was performed in basic aqueous solution using excess

$KMnO_4$[11]. This procedure gave **607** pure in 67% yield as determined from $^1H$ NMR.




*Scheme 6.1*

Deprotection of **607** by reflux in concentrated HI gave 1-hydroxybenzene-2,6-dicarboxylic acid (**608**) in 92% yield after crystallization from $H_2O$. Compound **608** was readily converted nearly quantitative in its dimethyl ester analogue by reaction with two equivalents of diazomethane[12]. This whole procedure gave **609** in 30% overall yield, starting from **604**, as white crystalline material, pure according to $^1H$, $^{13}C$ NMR and a melting point which was the same as the literature value[12]. In the last step of the preparation of ligand **610**, diester **609** was allowed to react with two equivalents of **538** in refluxing MeOH. This condensation reaction went rather slowly but after 5 days of reflux, 80% of **610** was formed which was purified using chromatographic methods to provide 53% of **610**. This ligand was pure according to $^1H$, $^{13}C$ NMR and HRMS analysis. It gave one spot on TLC ($SiO_2$, $MeOH/CH_2Cl_2$ 1 : 3, $R_f$ = 0.35).

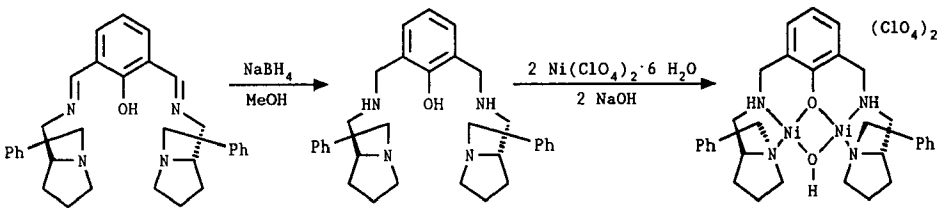
In order to prepare a dinuclear nickel complex derived from ligand **610**, it was allowed to react with two equivalents of NaOH and $Ni(ClO_4)_2 \cdot 6H_2O$ in refluxing methanol. Unexpectedly, no complex could be isolated and only starting ligand was recovered. Modifications of this procedure using other bases (NaOEt, NaH), other solvents (EtOH, THF) or $Ni(OAc)_2 \cdot 4H_2O$ gave no better results. Sofar we have not succeeded in incorporating two Ni(II) ions in ligand **610**; instead only starting ligand could be recovered. A possible explanation for this behavior can be the difficulty of deprotonating the amides, in protic solvents, by bases like NaOH or NaOEt to provide a trianionic species. In aprotic solvents like THF, the mono sodium salt of the ligand does not dissolve and a second and third deprotonation by NaH does not occur. Therefore stronger bases like butyl lithium are required.

If one of the amides is not deprotonated coordination may occur at the amide oxygen atom and thus the amine or phenol anchor cannot efficiently participate in the coordination of the metal. As a consequence no stable complex can be formed. An example can be seen in complex **602** (fig. 6.2) where no double deprotonation occurred. To avoid this coordination by the amide oxygen atom, the complex should be prepared in anhydrous solvents using nonhydrated Ni(II) salts[13].

Our second approach to prepare a ligand without imine functionalities was the conversion of the bis imine containing ligand into a bis amine ligand. This strategy, although much easier to accomplish, was not our first choice because of the greater reactivity of secondary amines towards oxidation, compared to amides. This conversion was easy achieved by $NaBH_4$ reduction of **548** in methanol at room temperature (scheme 6.2).

Pure bisamine ligand **612** was obtained almost quantitatively as judged by $^1H$ and $^{13}C$ NMR in which the imine hydrogens at approximately 8.0 ppm had disappeared completely and a new signal at 3.80 ppm was found for the four methylene hydrogens. This was not further purified but was allowed to react at once with two equivalents of $Ni(ClO_4)_2 \cdot 6H_2O$ and NaOH in refluxing

ethanol. In this way the corresponding complex **613** could be obtained as a dihydrate in 38% yield as a dark red powder. Analysis of **613** gave a formula of $C_{32}H_{40}N_4Ni_2Cl_2O_{10} \cdot 2H_2O$, thereby indicating that two Ni(II) ions are incorporated into the ligand.

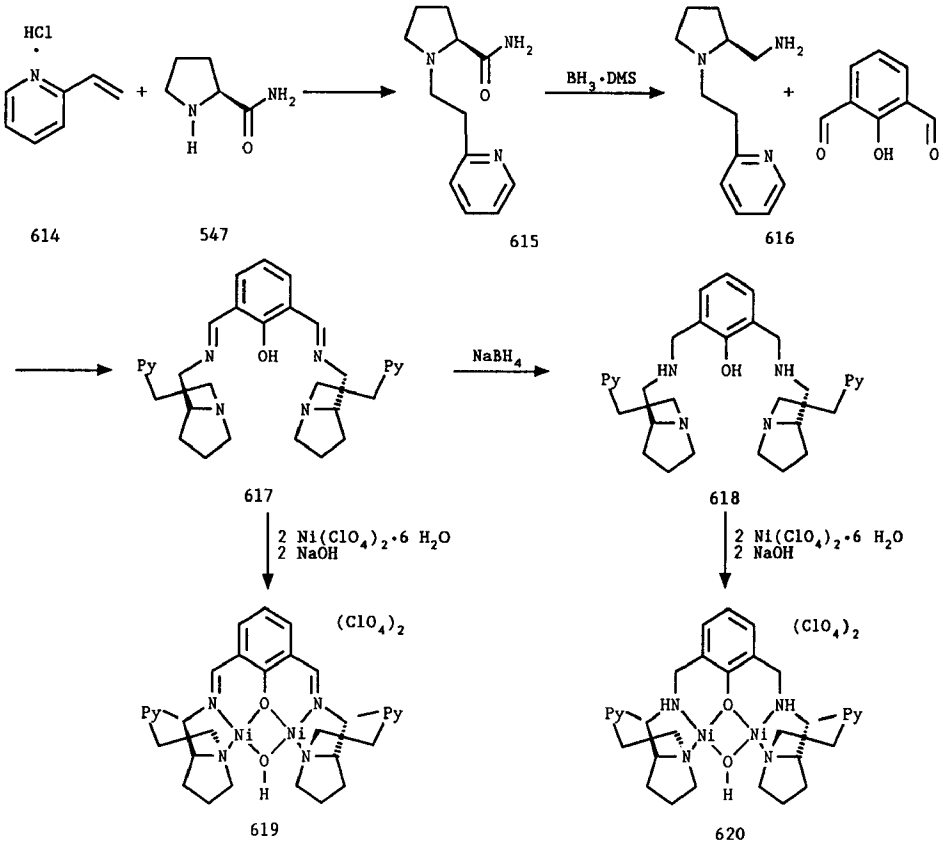



*Scheme 6.2*

Several examples are known in which related dinucleating amine ligands have been prepared by reduction of the imine double bonds[14]. Using this procedure the imine functionality is replaced by a more robust amine bond, which is less prone to hydrolytic cleavage.

### 6.2.2. *Introduction of an additional coordinating ligand*

The second ligand modification follows from the requirement of introducing an additional coordinating group into the ligand. If we look at the molecular structure, as depicted in figure 5.9 (p. 131), we see that the benzyl groups have different conformations. One group points to the Ni nuclei whereas the other points away from these nuclei. These groups are well suited for replacement by 2-picolinyl moieties (pyridine analog of benzyl) which can coordinate by their nitrogen atoms to the Ni(II) nuclei. In order to achieve this, a heptadentate ligand has to be prepared which can form dinuclear Ni(II) complexes with penta coordination around each Ni(II) ion. The synthesis of this ligand is outlined in scheme 6.3. For the ease of preparation, the methylene bridge between the pyridine and prolinamide is replaced by an ethylene bridge.




*Scheme 6.3 (Py = 2-pyridyl)*

In the first step, the hydrochloride salt of 2-vinylpyridine (**614**) reacted in a Michael-type reaction with (S)-prolinamide (**547**) in refluxing $H_2O$. This provided the tri-nitrogen containing compound **615**, as pure white crystalline material in 68% yield. Although we did not prove that racemization had not occurred during this step, it is reasonable to assume that this did not happen because these compounds are stable under acidic conditions.

Reduction of the amide in **615** to the corresponding amine **616** could not be accomplished by $LiAlH_4$ or $BH_3 \cdot THF$. These reagents gave both

cleavage and reduction of the pyridine moiety. However, when $BH_3 \cdot$ dimethylsulfide was used[15] as a milder reducing agent, 70% of the tris-amine **616** was obtained after distillation. Similar reduction of substituted prolinamids were carried out by Mukaiyama without racemization under these conditions[16]. This chiral amine, which was pure according to $^1H$ and $^{13}C$ NMR is rather unique in having a pyridine, a tertiary amine and a primary amine functionality in one molecule. Two equivalents of **616** were subsequently allowed to react with one equivalent of 1-hydroxybenzene-2,6-dicarboxaldehyde (**228**) in methanol to provide the bis imine **617**, which was not isolated but treated in situ with $NaBH_4$ to provide the corresponding amine **618** in nearly quantitative yield sufficiently pure for further use. Complexation of two Ni(II) ions into ligands **617** and **618** was easily achieved by reaction of these ligands with two equivalents of $Ni(ClO_4)_2 \cdot 6H_2O$ and NaOH in refluxing methanol. Isolation and crystallization of both complexes from $EtOH/H_2O$ mixtures provided complexes **619** and **620** as dark green crystalline material in 53 and 79% yield respectively. Analysis for both complexes showed that two Ni(II) ions probably bridged by a phenoxy and hydroxy moiety giving rise to penta coordinated complexes were present in each ligand.

Penta coordination is a commonly observed coordination number around Ni(II). Some examples are known in which the same donor set $N_3O_2$ as present here form five coordinated Ni(II) complexes[17]. Zakrzewski and Sacconi[18] reported the synthesis and characterization of a mononuclear Ni(II)LBr complex where L contained the same donor ligands (imine, pyridine, tertiary amine) as in **619** giving a penta coordinated complex.

However, no dinuclear Ni(II) complexes are known in which chiral ligands with a $N_3O_2$ donor set are present. In order to get a final proof of the exact structure of these complexes, **620** was analyzed by X-ray diffraction.

### 6.3 *Molecular structure of 620*

For a general introduction to Ni(II) coordination see section 5.8. Crystallization of complex **620** from a $H_2O$/EtOH mixture provided green, needle shaped, crystals which were suitable for an X-ray analysis. The structure has not yet been solved completely and the present R index is 0.067 so the results presented here are preliminary.

The complex crystallized in the orthorhombic space group $P2_12_12_1$ with unit cell dimensions of a = 8.813(1), b = 19.116(2) and c = 23.712(4) Å. The molecular structure with adopted numbering scheme is shown in fig. 6.3. Some selected bond distances and angles are given in table 6.1. Each nickel ion is surrounded by a $N_3O_2$ donor set to give five coordinated nickel(II). The five donor atoms adopt a distorted square-pyramidal arrangement such that O(1), O(2), N(2), N(3), and O(1), O(2), N(4), N(5) form the basel planes around the nickel ions. The maximum deviation from these planes is 0.01 Å. The metal is positioned 0.32(2) Å and 0.37(5) Å out of these planes towards the apical nitrogens N(1) and N(6). The Ni - Ni distance in **620** is 3.079(2) Å which is substantially longer than the Ni - Ni distance in **550** (2.849 Å). The cationic part of the complex has $C_2$ symmetry around the O(1) - O(2) - C15 axis.

By introducing this extra coordinating pyridine ligand (compared to **550**), we expect that higher oxidation states of nickel will be better stabilized. Furthermore higher "asymmetry" is found now around the Ni(II) nuclei which may influence the stereochemical control of the epoxidation reactions.

### 6.4 *Cyclic Voltammetry*

Reversible oxidation and reduction of Ni(II) has to take place during a catalytic epoxidation cycle where the nickel complexes are involved. As the nature of the intermediates is not established for either mono- or dinuclear nickel complexes, Ni(III), Ni(IV)-oxo, Ni(III)ONi(III) etc. might be involved[1].

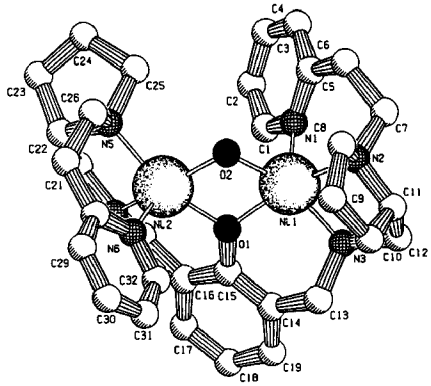



*Figure 6.3: Molecular structure of **620** with adopted numbering scheme (counter ions are omitted for clarity).*

*Table 6.1:* *Selected interatomic distances (Å) and angles (deg) for **620***

| | | | |
|---|---|---|---|
| Ni(1) - Ni(2) | 3.079(2) | O(1) - Ni(1) - O(2) | 77.4(3) |
| Ni(1) - O(1) | 1.995(8) | O(1) - Ni(1) - N(3) | 88.5(3) |
| Ni(1) - O(2) | 1.961(5) | O(1) - Ni(1) - N(2) | 162.1(3) |
| Ni(1) - N(1) | 2.006(5) | O(1) - Ni(1) - N(1) | 102.3(3) |
| Ni(1) - N(2) | 2.070(5) | N(1) - Ni(1) - N(2) | 95.5(2) |
| Ni(1) - N(3) | 2.058(6) | N(2) - Ni(1) - N(3) | 85.1(2) |
| Ni(2) - O(1) | 2.001(8) | N(1) - Ni(1) - N(3) | 104.4(2) |
| Ni(2) - O(2) | 1.973(5) | N(1) - Ni(1) - O(2) | 95.6(2) |
| Ni(2) - N(4) | 2.078(11) | N(2) - Ni(1) - O(2) | 103.0(2) |
| Ni(2) - N(5) | 2.035(11) | N(3) - Ni(1) - O(2) | 157.6(2) |
| Ni(2) - N(6) | 2.040(10) | O(1) - Ni(2) - O(2) | 77.0(3) |
| | | O(1) - Ni(2) - N(4) | 90.6(4) |
| | | O(1) - Ni(2) - N(5) | 156.8(4) |
| | | O(1) - Ni(2) - N(6) | 106.6(4) |
| | | O(2) - Ni(2) - N(4) | 158.8(4) |
| | | O(2) - Ni(2) - N(5) | 99.4(3) |
| | | O(2) - Ni(2) - N(6) | 99.6(4) |
| | | N(4) - Ni(2) - N(5) | 85.2(4) |
| | | N(4) - Ni(2) - N(6) | 100.7(4) |
| | | N(5) - Ni(2) - N(6) | 99.6(4) |
| | | Ni(1) - O(1) - Ni(2) | 100.8(4) |
| | | Ni(1) - O(2) - Ni(2) | 103.0(2) |

In order to obtain more information about the ligand stabilization of these nickel species, complexes **550**, **613**, **619** and **620** (fig 6.4) were investigated by cyclic voltammetry with regard to their electrochemical properties.

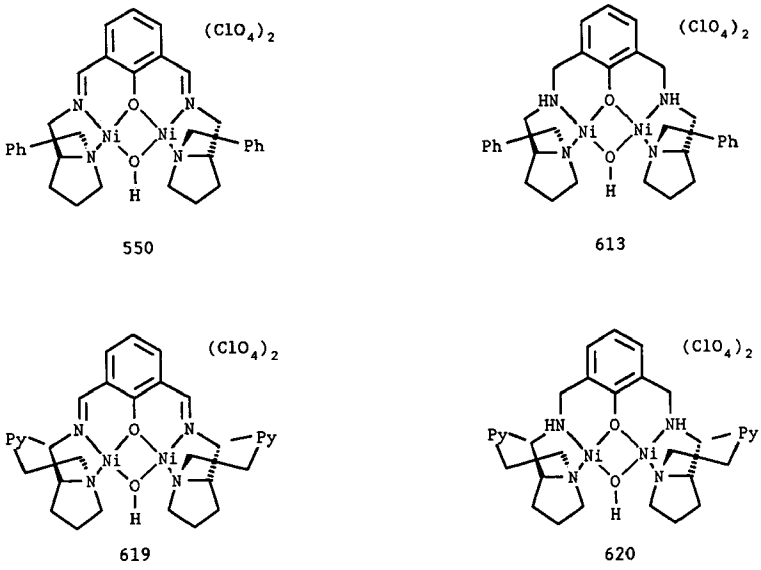



*figure 6.4 (Py = 2-pyridyl)*

The stabilization of high oxidation states of nickel requires ligands with high electron density and/or one or more negative charges in order to allow for some charge delocalization from the ligand to the metal. Both Ni(III) and Ni(IV) complexes are usually found in octahedral environments. These complexes are generally highly reactive leading to oxidation of a variety of organic substrates to form the more stable Ni(II) complexes. Some stable Ni(III) complexes with aliphatic diamines have been prepared by chemical oxidation of Ni(II) species[19]. With ethylene diamine and 1,2-diaminopropane, both genuine Ni(III) complexes or mixed valence Ni(II) - Ni(IV) dimer complexes were obtained[20]. Several amine, imine and oxy-ligated mononuclear

Ni(II) complexes were investigated by electrochemical methods such as cyclic voltammetry. The oxidation potential of the Ni(II)/Ni(III) couple varies over a range of at least 1.8 V by changes in coordinating ligands[21]. Kochi and co-workers[22] found that there was no correlation of the catalytic efficiency of the Ni(II) complexes of various ligands with the ease of oxidation as measured by the electrode potential for the Ni(II)/Ni(III) interconversion.

All measurements were performed in acetonitrile in a dry box under an inert atmosphere using a one compartment cell, with a Pt-wire working electrode (l = 3 - 4 mm, Ø = 0.65 mm), a Pt-wire counter and a silver-wire reference electrode with 0.1 M $Bu_4NClO_4$ as the supporting electrolyte. No corrections for internal resistance were made. All potentials are given vs. the Ferrocene/Ferrocenium$^+$ ($Fc/Fc^+$) couple[23].

Complexes **550**, **613** and **620** could be oxidized irreversibly at +1.16, +0.87 and +0.74 respectively (figure 6.5a). Indicating that the oxidized species are unstable. Only **613** and **620** gave a small reduction peak at 0.03 and 0.05 V at the subsequent reductive sweep.

Complex **619** could be oxidized reversible at -0.86 V (50 mV/s) (figure 6.5b). Whether this is a one or two electron oxidation was not investigated but in other dinuclear hydroxy-phenoxy bridged Ni(II) complexes only one electron oxidation was found[24]. This reversible oxidation/reduction observed at a scan rate of 50 mV/s indicates a half-life time for the oxidized compound of at least $t_{½} \geq 0.2$ s[25]. When **619** was reduced, two reduction waves were found at -1.75 and -1.97 V, which were not investigated for reversibility.

It can be concluded from these data that only the ligand present in complex **619** is able to stabilize an oxidized Ni(II) species, probably Ni(III). This means that both an imine and a pyridine ligand are necessary for stabilization. When one of these ligating groups is removed, as in complexes **550** and **620**, or both are removed, as in complex **613**, no stable Ni(III) species can be formed under cyclic voltammetric conditions. Because of the requirement of electron donation for stabilization of higher nickel oxidation

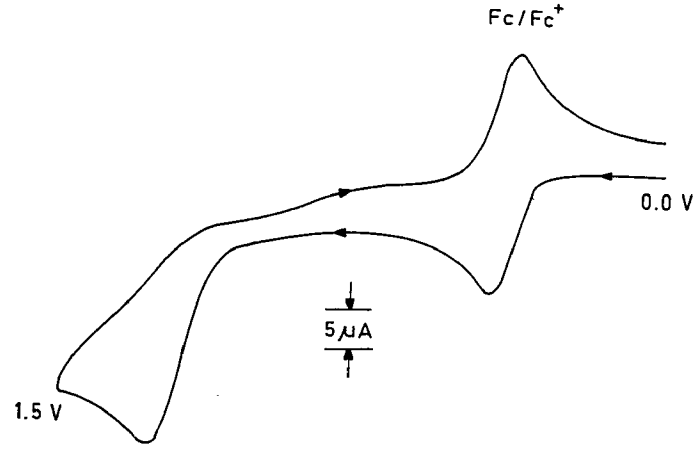



*Figure 6.5.a: Cyclic voltammogram of **620** in $CH_3CN$ at 50 mV/s (and $Fc/Fc^+$ couple).*

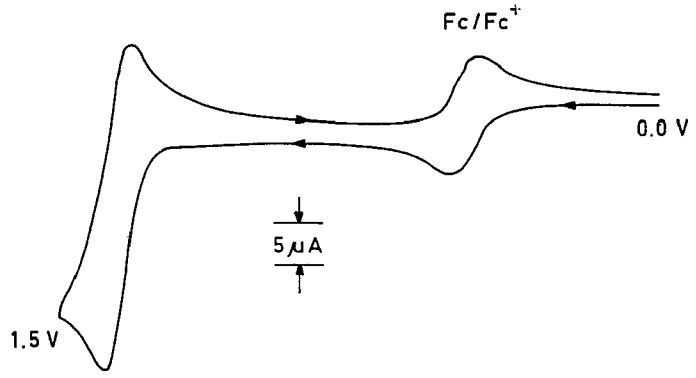



*Figure 6.5.b: Cyclic voltammogram of **619** in $CH_3CN$ at 50 mV/s (and $Fc/Fc^+$ couple).*

*Table 6.2: Electrochemical data of the oxidation of complexes **550, 613, 619** and **620** in $CH_3CN$ vs. $Fc/Fc^+$ couple*

| | $E_{1/2}$ vs. $Fc/Fc^+$ | character |
|---|---|---|
| **550** | 1.16 | irrev. |
| **613** | 0.87 | irrev. |
| **619** | 0.86 | rev. |
| **620** | 0.74 | irrev. |

states, the penta coordinated complexes **619** and **620** are more stable than the tetra coordinated complexes **550** and **613** when oxidized. However, in spite of the better donating properties of an amine (as is present in **620**) compared to the imine[26] (in **619**), only complex **619** is able to stabilize higher oxidation states. A possible explanation for the irreversible oxidation of **613** and **620** as compared to **619** can be the greater vulnerability of a secondary amine towards oxidation compared to the imine functionality. The fate of the ligands and complexes (i.e. stability) under the actual epoxidation conditions has to be compared with these electrochemical results.

### 6.5 *Concluding remarks*

With several new dinuclear Ni(II) complexes now synthesized, characterized and their electrochemical properties investigated, the next thing we should do is to investigate and compare these different complexes in epoxidation reactions. Some preliminary results of this investigation showed that all the synthesized bis nickel(II) complexes could be used as catalysts in epoxidation reactions of aryl alkenes under phase-transfer conditions using t-BuOOH as the terminal oxidant (see chapter 5). In a first series of experiments with catalysts, **613**, **619**, and **620** all showed about the same order of activity and selectivity. However, no quantitative analysis was made.

With this investigation we have shown that various bis nickel(II) complexes can be used as catalysts in epoxidation reactions. However, little is understood about the mechanisms and lack of selectivity in these reactions (see section 5.10). Modification of the ligands can easily be done, but little is known about the necessary fine tuning of these ligands in order to obtain higher selectivity in the epoxidation reaction.

In the future other metal ions such as Mn(II), Fe(II), Co(II) etc. should be investigated with regard to their epoxidation ability using these kind of ligands. Especially Mn(II) is a likely candidate because of the recent results obtained by Jacobson and co-workers in asymmetric epoxidations by using

mononuclear Mn(II) complexes (see chapter 5)[27]. The presence of two metal ions in the catalyst might be used to activate dioxygen as the oxidant, as was found in bis Cobalt(II) complexes as described[28] in section 1.3.

## 6.6 *Experimental part*

For general remarks see section 2.9. Cyclic Voltammetry was carried out by Hans Roedelof with a Parc-174 polarograph directed by a 175 Programmer (Parc) or by a Parc 273 potentiostat. The solutions were freshly prepared in $CH_3CN$ (Aldrich, P.A. quality) with 0.1 M $Bu_4NClO_4$ as the electrolyte. 2-Vinylpyridine hydrochloric salt was prepared by leading HCl (g) into an etheral solution of 2-vinylpyridine.

**1-Hydroxy-6-methylbenzene-2-carboxaldehyde (605)**

This compound was prepared following a procedure described in ref. 9. Starting from 30 g (0.28 mol) *o*-cresol, 26 g crude material was isolated after steam distillation. The oil was distilled at reduced pressure (91-93°C, 16 mm Hg) to yield 22.1 g (58%) of **605** as a colourless oil (lit. b.p. 211°C/760 mm Hg). $^1$H NMR($CDCl_3$): $\delta$ 2.31 (s, 3H), 6.67-7.11 (m, 1H), 7.41 (d, 2H), 10.24 (s, 1H), 11.67 (s, 1H).

**1-Methoxy-6-methylbenzene-2-carboxaldehyde (606)**

This compound was prepared according to known procedures described in ref. 10. Starting from 10.0 g (74 mmol) **605**, 3 g NaOH and 9.3 g (75 mmol) dimethyl sulfate, there was obtained 10.1 g (91%) of **606** after distillation at 110-115°C/16 mm Hg, which was pure according to $^1$H NMR (lit[29]. b.p. 118°C/12 mm Hg). $^1$H NMR($CDCl_3$): $\delta$ 2.24 (s, 3H), 3.79 (s, 3H), 6.84-7.74 (m, 3H), 10.37 (s, 3H).

**1-Methoxy-isophthalic acid (607)**

This compound was prepared according to the procedure described in ref. 11. Starting with 1.5 g (1 mmol) **606**, 0.7 g $Na_2CO_3$ and 7.0 g $KMnO_4$, 1.3 g (66%) of **607** was obtained as a white solid which was not further purified but deprotected as such in the next step. $^1$H NMR($CDCl_3$/$CD_3OD$): $\delta$ 4.38 (s, 3H), 7.51-7.89 (m, 1H), 8.45 (d, 2H).

**1-Hydroxy-isophthalic acid (608)**

A solution of 1.3 g (6.6 mmol) **607** in 30 ml 30% aqueous HI was refluxed for 30 min.. After this period the HI and MeI were removed by distillation in vacuo. This procedure

was repeated several times untill a white solid material was obtained. Crystallization of this solid from $H_2O$ yielded 1.05 g (87%) of diacid **608** as white crystals which were dried over $P_2O_5$. m.p. 246-247.5°C (dec.) (lit[11]. m.p. 245-247°C); $^1$H NMR($CD_3OD$): $\delta$ 6.96 (t, $J$ = 7.5 Hz, 1H), 8.08 (d, 2H); $^{13}$C NMR ($CD_3OD$): $\delta$ 117.69, 119.86, 137.96, 163.17, 171.16 ppm.

**1-Hydroxybenzene-2,6-dicarboxymethyl (609)**

This compound was prepared according to a literature procedure described in ref. 12. Starting from 0.50 g (2.7 mmol) of **608** and diazomethane in ether, 0.43 g (74%) of **609** was obtained after recrystallization from MeOH as white crystalline material. m.p. 70.2-71.5°C (lit. m.p. 70-72°C); $^1$H NMR($CD_3OD$): $\delta$ 3.95 (s, 6H), 6.95 (t, $J$ = 7.9 Hz, 1H), 8.02 (d, 2H); $^{13}$C NMR ($CD_3OD$): $\delta$ 52.93, 117.46, 119.62, 137.17, 162.10, 169.31 ppm.

**1-Hydroxybenzene-2,6-bis[N-[(S)-2-(aminomethyl)-1-benzylpyrrolidine]]carboxamide (610)**

A solution of 210 mg (1 mmol) **609** and 380 mg (2 mmol) of (S)-2-(aminomethyl)-1-benzyl-pyrrolidine (**538**) in 30 ml MeOH was heated at reflux for 5 days. After this period the MeOH was evaporated in vacuo and the crude oil was purified by chromatography over Silicagel using $CH_2Cl_2$/MeOH (3 : 1) as the eluent. This gave 280 mg (53%) of **610** as a colourless oil, which was pure according to $^1$H and $^{13}$C NMR. $^1$H NMR($CDCl_3$): $\delta$ 1.58-1.64 (m, 6H), 1.85-2.00 (m, 2H), 2.19-2.29 (m, 2H), 2.83 (br s, 2H), 2.95-3.04 (m, 2H), 3.23-3.30 (m, 2H), 3.65 (dd, $J$ = 13 Hz, $J$ = 177 Hz, 4H), 3.63-3.76 (m, 2H), 6.89 (t, $J$ = 8 Hz, 1H), 7.15-7.33 (m, 10H), 7.85 (d, $J$ = 8 Hz, 2H), 8.10 (br s, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.64, 28.14, 40.90, 54.05, 58.26, 62.17, 117.54, 117.96, 126.81, 128.03, 128.40, 132.64, 138.44, 161.12, 167.77. HRMS calculated for $C_{32}H_{38}N_4O_3$: 526.294, found: 526.293 ppm.

**(S)-1-(2-(2-Pyridyl)ethyl)-pyrrolidine-2-carboxamide (615)**

A solution of 5.0 g (35 mmol) of 2-vinylpyridine hydrochloride (**614**) and 4.03 g (35 mmol) (S)-prolinamide (**547**) in 100 ml $H_2O$/MeOH (5 : 1) was refluxed for 16 h.. The solution was neutralized with excess $NaHCO_3$ and the water layer was extracted with $CH_2Cl_2$ (3 x 50 ml). The combined $CH_2Cl_2$ layers were dried over $MgSO_4$, filtered and evaporated to dryness in vacuo to provide a white solid which was crystallized from toluene. This yielded 5.2 g (68%) of **615** as white crystalline material. m.p. 135.3-136.7°C; $[\alpha]^{578}_{20}$ = -108.8° (c 1.0, $CH_3OH$); $^1$H NMR($CDCl_3$): $\delta$ 1.50-1.78 (m, 3H), 1.94-2.09 (m, 1H), 2.17-2.28 (m, 1H), 2.61-2.72 (m, 1H), 2.76-2.97 (m, 3H), 2.99-3.14 (m, 2H), 6.48 (br s, 1H), 6.92-7.08 (m, 3H), 7.41-7.50 (m, 1H), 8.36 (d, $J$ = 5 Hz, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 23.91, 30.29, 37.17, 53.38, 54.88, 67.45,121.04, 122.92, 136.04, 148.89, 159.66, 178.30 ppm. HRMS calculated for $C_{12}H_{18}N_3O$:

219.126, found: 219.125. Analysis calculated for $C_{12}H_{18}N_3O$: C: 65.74, H: 7.81, N: 19.16, found: C: 65.46, H: 7.79, N: 18.90.

**(S)-2-Aminomethyl-1-(2-(2-pyridyl)ethyl)-pyrrolidine (616)**

To a solution of 25 ml 2 M $BH_3 \cdot$ DMS in THF, cooled with an ice bath to 0°C was slowly added 2.50 g (11.4 mmol) of **615**, dissolved in 30 ml THF. This mixture was refluxed for 12 h. after which period it was cooled to 0°C. Next, 10 ml MeOH was added cautiously and stirring continued for 1 h.. After this time gaseous HCl was used to saturate the THF with HCl until a pH < 2. The mixture was subsequently heated at reflux for one hour and an additional 50 ml of MeOH was added and the mixture was evaporated to dryness in vacuo to give crude **616** as an oil. This oil was dissolved in 20 ml NaOH (4 N) and the water layer was washed with $CH_2Cl_2$ (3 x 30 ml). The combined $CH_2Cl_2$ layers were dried over $Na_2SO_4$, filtered and evaporated to dryness in vacuo to give an oil which was distilled at 170°C (0.05 mm Hg) using a Kugelrohr distillation apparatus to yield 1.63 g (70%) of **616** as a colourless oil. $^1$H NMR($CDCl_3$): $\delta$ 1.02 (br s, 2H), 1.36-1.75 (m, 4H), 2.03-2.18 (m, 1H), 2.18-2.27 (m, 1H), 2.35-2.55 (m, 3H), 2.68-2.88 (m, 2H), 2.92-3.12 (m, 2H), 6.85-7.05 (m, 2H), 7.35-7.47 (m, 1H), 8.35 (br s, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.74, 27.48, 37.36, 43.83, 53.78, 54.12, 120.60, 122.70, 135.67, 148.71, 160.18 ppm. HRMS calculated for $C_{12}H_{19}N_3$: 205.110, found: 205.108.

**2,6-bis[N-[(S)-1-benzylpyrrolidine-2-yl]aminomethyl]-1-hydroxybenzene (612)**

A solution of 150 mg (1 mmol) 1-hydroxybenzene-2,6-dicarboxaldehyde (**228**) and 380 mg (2 mmol) (S)-2-(aminomethyl)-1-benzylpyrrolidine (**538**) (see chapter 5) in 30 ml MeOH was stirred for 1 h. at room temperature. Next, 150 mg (4 mmol) $NaBH_4$ was added over an one hour period in six portions. After one additional hour of stirring, the MeOH was evaporated in vacuo and the crude oil was dissolved in 30 ml $CH_2Cl_2$. This $CH_2Cl_2$ was washed with water (2 x 20 ml), dried over $Na_2SO_4$, filtered and evaporated to dryness in vacuo to provide 450 mg (90%) of **612** as an oil sufficiently pure according to NMR for further use. $^1$H NMR($CDCl_3$): $\delta$ 1.66-1.78 (m, 6H), 1.78-1.95 (m, 2H), 2.15-2.23 (m, 2H), 2.56-2.73 (m, 6H), 2.91-2.95 (m, 2H), 3.61 (dd, $J$ = 13,2 Hz, $J$ = 174 Hz, 4H), 3.80 (s, 4H), 6.71 (t, $J$ = 7.3 Hz, 1H), 6.99 (d, $J$ = 7.3 Hz, 2H), 7.23-7.30 (m, 10H); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.95, 28.96, 51.11, 51.50, 54.55, 59.10, 63.19, 118.16, 124.57, 126.64, 127.72, 128.03, 128.53, 139.72, 156.47 ppm.

**2,6-Bis[N-[(S)-1-(2-(2-pyridyl)ethyl)pyrrolidine-2-yl]aminomethyl]-1-hydroxybenzene (618)**

This compound was prepared following the same procedure as described for **612**. Starting from 150 mg (1 mmol) of **228** and 412 mg (2 mmol) of **617**, 487 mg (93%) of **618** was obtained as an oil, sufficiently pure for further use, according to $^1$H NMR.

$^1$H NMR($CDCl_3$): $\delta$ 1.61-1.72 (m, 6H), 1.83-1.87 (m, 2H), 2.19-2.24 (m, 2H), 2.50-2.61 (m, 8H), 2.87-2.93 (m, 4H), 3.09-3.18 (m, 4H), 3.73 (s, 4H), 6.66 (t, $J$ = 7.3 Hz, 1H), 6.92-7.11 (m, 6H), 7.46-7.52 (m, 2H), 8.45 (d, $J$ = 4.4 Hz, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 23.15, 28.77, 37.51, 50.98, 51.55, 53.96, 54.33, 63.12, 118.02, 120.90, 123.04, 124.34, 127.56, 135.95, 148.95, 156.40, 160.43 ppm. No HRMS could be obtained because of the instability of **618** under EI conditions.

**$\mu$-Hydroxo-$\mu$-[2,6-Bis[N-[(S)-(1-(2-(2-pyridyl)ethyl)pyrrolidine-2-yl]aminomethyl]phenolato] bisnickel(II)perchlorate (620)**

A solution of 500 mg (0.94 mmol) **618**, 76 mg NaOH and 690 mg (1.9 mmol) $Ni(ClO_4)_2 \cdot 6H_2O$ in 30 ml EtOH was refluxed for 3h. After this time, the solution was evaporated to dryness in vacuo and the green residue was crystallized from EtOH/$H_2O$ to yield 620 mg (77%) of **620** as green needles which were suitable for an X-ray analysis. Analysis calculated for $C_{32}H_{44}Cl_2N_6Ni_2O_{10} \cdot CH_3CH_2OH$: C: 45.02, H: 5.55, Cl: 7.82, N: 9.26, Ni: 12.94, found: C: 44.39, H:5.48, Cl: 8.09, N: 9.21, Ni: 12.67.

**$\mu$-Hydroxo-$\mu$-[2,6-Bis[N-[(S)-(1-(2-(2-pyridyl)ethyl)pyrrolidine-2-yl]formimidoyl]phenolato bisnickel(II)perchlorate (619)**

A solution of 150 mg (1 mmol) **228** and 408 mg (2 mmol) of **616** in 30 ml $CH_2Cl_2$ was stirred for 1h.. Next $Na_2SO_4$ was added and after 15 min. the $CH_2Cl_2$ was filtrated and evaporated to dryness in vacuo. The oily residue was dissolved in 30 ml EtOH and 80 mg (2 mmol) NaOH and 730 mg (2 mmol) $Ni(ClO_4)_2 \cdot 6H_2O$ was added. The mixture was refluxed for 2.5 h. and the solvent was subsequently evaporated in vacuo to give dark green material which was crystallized from EtOH to yield 560 mg (65%) of **619** as dark green crystalline material. Analysis calculated for $C_{32}H_{40}Cl_2N_6Ni_2O_{10}$: C: 44.85, H: 4.67, Cl: 8.29, N: 9.81, Ni: 13.71, found: C: 44.34, H: 4.64, Cl: 7.89, N: 9.66, Ni: 13.56.

**$\mu$-Hydroxy-$\mu$-[2,6-Bis[N-[(S)-(1-benzylpyrrolidine-2-yl]aminomethyl]phenolato bisnickel(II)perchlorate (613)**

A solution of 249 mg (0.5 mmol) **612**, 40 mg (1 mmol) NaOH and 365 mg (1 mmol) of $Ni(ClO_4)_2 \cdot 6H_2O$ in 30 ml EtOH was refluxed for 3 h.. After this time, the red solution was evaporated to dryness in vacuo to give a red powder, which was crystallized by diffusion of diisopropylether in a methanol solution of this material to yield 170 mg (41%) of complex **613** as dark red crystalline material. Analysis calculated for $C_{32}H_{40}Cl_2N_4Ni_2O_{10} \cdot 2H_2O$: C: 44.45, H: 5.09, N: 6.48, Ni: 13.52, found: C: 44.67, H: 5.16, N: 6.39, Ni: 13.61.

**Cyclic voltammetric measurements**

Cyclic Voltammetry was carried out with a Parc 273 potentiostat. All measurements were carried out in an one compartment cell using a Pt-wire (3-4 mm, cross section 0.65 mm) as a working electrode, a larger Pt-wire as auxiliary electrode and a Ag/AgCl reference electrode. In order to bring the working and reference electrodes in close proximity, a Luggin capillary was used. The solutions were freshly prepared in $CH_3CN$ (Aldrich, P.A. quality) with 0,1 M $Et_4N^+ClO_4^-$ twice crystallized from ethylacetate/$CHCl_3$, as supporting electrolite in a drybox in an inert nitrogen atmosphere. All potentials are determined using ferrocene as an internal standard. No corrections for internal resistance were made.

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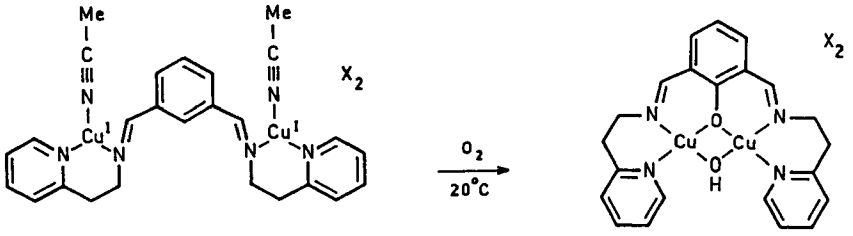
## SUMMARY

So far hydroxylation and epoxidation using molecular oxygen in combination with transition metal catalysts is limited in scope and selectivity A small number of transition metal complexes have been demonstrated to be able to bind and to activate molecular oxygen for performing chemical reactions. Recent advances in the synthesis of organic ligands that are capable of binding several metal ions and new insights in reaction patters of oxidations in biological systems using molecular oxygen formed the background of this investigation.

This thesis concerns with the synthesis, characterization and study of the activity of new bimetallic oxidation catalysts which are designed to carry out specific chemical conversions using molecular oxygen or mono-oxygen donors such as sodium hypochlorite or tertiar-butylhydroperoxide.

In chapter 1 a brief overview is presented of the possible binding modes and activation of oxygen on organometallic complexes. Also some examples of the use of bimetallic catalysts in oxidation reactions as well as their advantages and disadvantages are discussed.

Chapter 2 deals with the synthesis of a new ligand system that is capable of binding two copper(I) ions. Each copper(I) ion in this complex is coordinated by three nitrogen donor groups giving a trigonal planar arrangement which is seldom found for copper(I) complexes. This represents the first example of a dinuclear copper(I) complex with mono as well as bidentate ligands. When this complex is oxidized, using molecular oxygen, a remarkable specific arene hydroxylation of the




*scheme 1*

ligand is found (scheme 1). The reactivity of this bis copper(I) complex resembles the reactivity of bis copper(I) containing enzymes such as tyrosinase which are able to hydroxylate phenols.

A mechanistic investigation of this hydroxylation is presented in chapter 3. A number of dinucleating ligands for copper were synthesized in which the C-1 position, most vulnerable for arene hydroxylation, is substituted. The ligand with bromo and methoxy substituents at the C-1 position turned out to give the same hydroxylation reaction as was observed for the unsubstituted case. Simultaneously an oxidative debromination and demethoxylation takes place. The unique arene demethoxylation was investigated using an $^{18}O$ labelled ligand, $^{18}O_2$ and $CD_3OD$. By performing these labelling experiments we gained information about the nature of the intermediates acting in the arene hydroxylation using two copper centra and molecular oxygen. It was found that a nucleophilic peroxo-dicopper(II) species might be an important intermediate which contradicts the proposal of an electrophilic peroxo-dicopper(II) species that is suggested in literature for a related hydroxylation reaction.

In chapter 4 the synthesis of a ligand is described in which a hydroquinone moiety is incorporated that should act as an electron shunt to the copper(II) centra in the dinuclear copper complex derived thereof. When this ligand was reacted with two equivalents of copper(II) salts an unexpectedly stable hydroquinone bridged bis copper(II) complex was obtained. This complex represents the first example of a stable hydroquinone bridged dinuclear copper(II) complex. Although the internal electron transfer from the hydroquinone moiety to the Cu(II) centra did not occur, this complex appeared to be an efficient catalyst for the oxidation of external hydroquinones and $\alpha$-hydroxy ketones using molecular oxygen as the terminal oxidant.

Unfortunately no catalytic oxygen transfer towards external substrates could be achieved using these bis copper(II) complexes. Therefore it was decided to look at another metal nucleus.

During our research mononuclear nickel(II) complexes were reported in the literature to catalyze the epoxidation of olefins with oxidants like sodium hypochlorite and iodosylbenzene. A dinuclear nickel species was proposed as a possible active intermediate in these reactions. Furthermore, epoxidation reactions are interesting from a stereochemical point of view: two new stereogenic centra are created in one step starting from prochiral olefins.

For these reasons we designed and synthesized new dinuclear nickel(II) complexes. Chapter 5 deals with the synthesis and characterization of new chiral bis nickel(II) complexes. These complexes were also investigated with respect to their catalytical activity in epoxidation reactions of aryl alkenes using sodium hypochlorite and tertiar-butylhydroperoxide. Catalytic epoxidation reactions could be achieved with these nickel(II) complexes, however no asymmetric induction in the epoxides was found. The examples described here are the first (chiral) bis nickel(II) complexes which are investigated on their catalytical properties in epoxidation reactions. The use of tertiar-butylhydroperoxide in combination with nickel catalysts is unique. Turnover numbers and selectivities are comparable with the mononuclear nickel(II) complexes

Finally, in chapter 6 some modifications of these chiral bis nickel(II) complexes are described in order to influence the reactivity and stereoselectivity in the epoxidation reactions favorably Several chiral bis nickel(II) complexes were investigated electrochemically by using cyclic voltammetric methods on their stability in higher oxidation states. Until now no clear improvements in selectivity and reactivity in epoxidation reactions of the dinuclear nickel complexes were found.

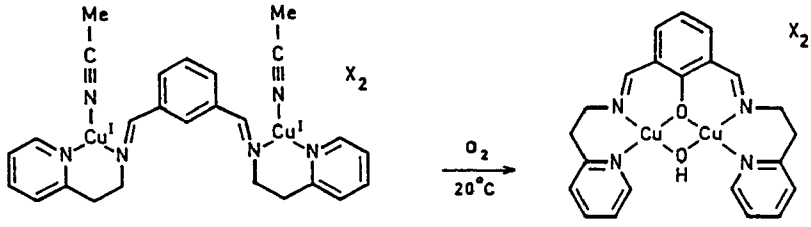
## SAMENVATTING

Tot nu toe zijn slechts een beperkt aantal methoden ontwikkeld om zuurstof te gebruiken in een direct proces om belangrijke chemische verbindingen zoals alcoholen of epoxiden te vormen. Slechts een gering aantal metaalcomplexen is in staat zuurstof te binden en te activeren om chemische reacties te bewerkstelligen. Nieuwe ontwikkelingen in de synthese van organische liganden die in staat zijn meerdere metalen te binden en nieuwe inzichten in het verloop van oxidatiereacties met zuurstof in biologische systemen vormen de achtergrond van dit onderzoek. Dit proefschrift beschrijft de synthese, de karakterisatie en de bestudering van de activiteit van nieuwe bimetallische oxidatiekatalysatoren die in staat zijn specifieke chemische conversies met moleculaire zuurstof of mono-zuurstof donoren te bewerkstelligen.

Hoofdstuk 1 begint met een kort overzicht van de mogelijke manieren van zuurstofbinding en activering aan organometaal complexen. Tevens wordt een aantal voorbeelden en de voor- en nadelen van het gebruik van bimetallische katalysatoren in oxidatie reacties besproken.

Hoofdstuk 2 beschrijft de synthese van een nieuw ligandsysteem dat in staat is twee koper(I) ionen te binden. Het bijzondere van dit bis-koper(I) complex is dat beide koper(I) ionen door "slechts" 3 stikstofatomen omringd worden. Dit is het eerste voorbeeld van een bis-koper(I) complex dat zowel bidentaat als monodentaat liganden bevat. Wanneer dit complex geoxideerd wordt met moleculaire zuurstof, blijkt onverwacht een specifieke areen-hydroxylering van het ligand op te treden (schema 1). Deze reactiviteit is te vergelijken met de reactiviteit van bis-koper

*schema 1*



bevattende enzymen zoals tyrosinase die in staat zijn externe substraten te hydroxyleren met moleculaire zuurstof.

Het mechanisme van deze bijzondere hydroxyleringsreactie wordt aan een nader onderzoek onderworpen in hoofdstuk 3. Hiervoor werden analoge liganden, met een broom en een methoxy substituent op het reactieve koolstof centrum, gesynthetiseerd. De bis-koper(I) complexen hiervan afgeleid gaven een oxidatieve dehalogenerings- respectievelijk een oxidatieve demethoxyleringsreactie te zien wanneer zij met moleculaire zuurstof reageerden. Deze unieke demethoxyleringsreactie werd nader onderzocht m.b.v. een $^{18}O$ gelabelled ligand, $^{18}O_2$ en $CD_3OD$. Door deze labellings experimenten werd inzicht verkregen in de aard van de intermediairen die in deze reactie voorkomen. Het bleek dat een nucleofiel peroxo-di-koper(II) complex waarschijnlijk als intermediair optreedt. Dit is in tegenstelling met het in de literatuur geponeerde electrofiele peroxo-di-koper(II) deeltje dat voorgesteld wordt als een belangrijk intermediair in een soortgelijke reactie. Bij pogingen om het met een methoxy groep gesubstitueerde bis-koper(I) complex kristallijn te verkrijgen werd onverwacht een coordinatiepolymeer verkregen dat een bijzondere helixstructuur vormde.

Aangezien de in hoofdstukken 2 en 3 beschreven kopercomplexen alleen zichzelf intern oxideerden werd vervolgens getracht een alternatief complex te maken dat in staat is externe substraten te oxideren. In hoofdstuk 4 wordt derhalve de synthese van een ligand beschreven waarin een hydrochinon eenheid is ingebouwd. Het bis-koper(II) complex hiervan afgeleid moet als katalysator voor externe substraatoxidatie fungeren. Het hydrochinon ligand wordt hierbij als electronoverdrachtsmiddel van externe reductoren naar de koper(II) centra gebruikt. Het bis-koper(II) complex van dit ligand bleek echter onverwacht stabiel. Een hydrochinon gebrugd bis-koper(II) complex kon worden geïsoleerd en gekarakteriseerd. Dit is het eerste voorbeeld van een stabiel hydrochinon gebrugd bis-koper(II) complex. Alhoewel de interne electronoverdracht niet plaats vond, bleek dit complex wel een goede katalysator voor de oxidatie van externe hydrochinonen en $\alpha$-hydroxyketonen m.b.v. zuurstof te zijn.

Het bleek echter niet mogelijk met deze bis-koper(II) complexen katalytisch zuurstof over te dragen op externe organische substraten, zodat besloten werd op een ander metaal over te gaan. Recent is gevonden dat mononucleaire Ni(II) complexen in staat zijn olefinen te epoxideren met zuurstofdonoren zoals natriumhypochloriet en iodosylbenzeen. Als mogelijk actieve katalysator in deze reacties wordt een dinucleair-nikkel complex voorgesteld. Verder is de epoxidatiereactie interessant, omdat in 1 stap twee nieuwe chirale centra worden gecreëerd. In hoofdstuk 5 wordt daarom de synthese en karakterisatie van nieuwe chirale bis-nikkel(II) complexen beschreven. Deze chirale bis-nikkel(II) complexen werden onderzocht op hun katalytische activiteit in epoxidatiereacties van arylalkenen m.b.v. NaOCl en t-BuOOH. Zij bleken actief te zijn in deze epoxidatiereacties, echter zonder enige inductie in de epoxides tot stand te brengen. Dit zijn de eerste (chirale) bis-nikkel(II) complexen die onderzocht zijn op hun katalytische activiteit in epoxidatiereacties. Het gebruik van t-BuOOH als oxidant in combinatie met nikkelkatalysatoren is uniek.

Tenslotte worden in hoofdstuk 6 enige modificaties van deze chirale bis Ni(II) complexen beschreven teneinde de reactiviteit en stereoselectiviteit in de epoxidatiereacties gunstig te beïnvloeden. De verschillende bis-Ni(II) complexen werden electrochemisch onderzocht m.b.v. cyclische voltammetrie op hun stabiliteit in de geoxideerde toestand. Tot nu toe werd er echter nog geen duidelijke verbetering in de selectiviteit en reactiviteit in epoxidatiereacties, met behulp van deze dinucleaire nikkel(II) complexen, gevonden.